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HYDRIDE REDUCTION OF 2-ALKOXYTETRAHYDROPYRANS.

by

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A THESIS

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The author is pleased to acknowledge the assistance and guidance of Dr. R. K. Brown, without whom this work would not have been possible.

The undersigned certify that they have read, and recommend possible.

to the Faculty of Graduate Studies for acceptance, a thesis entitled

I wish to thank Mr. R. N. Swindlehurst for infrared and nuclear magnetic resonance spectra, and Mrs. Darlene Mahlow for the carbon submitted by URIEL ENRIQUE DINER, in partial fulfilment of the and hydrogen analyses.
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A B S T R A C T

The hydrogenolysis of 2-alkoxy and 2-aryloxytetrahydropyrans by the mixed reagent $\text{AlCl}_3\text{-LiAlH}_4$ has been examined.

When a mixture of LiAlH_4 and acetal or ketal is treated with AlCl_3 with all reagents in equimolar proportions, the active reducing species is AlClH_2 . The relative reducing potency of the species AlH_3 , AlClH_2 and AlCl_2H , obtained by mixtures of LiAlH_4 and AlCl_3 in the proportions of 3:1, 1:1 and 1:3 respectively, is in the order $\text{AlH}_3 < \text{AlClH}_2 < \text{AlCl}_2\text{H}$.

The hydrogenolysis of 2-alkoxytetrahydropyrans provides products arising from both ring C-O bond cleavage and exo C-O bond cleavage (ring retention). The proportion of ring cleavage to ring retention depends upon the group (R) attached to the exo oxygen and increases in the order for R, $\text{CH}_3 < \text{C}_2\text{H}_5 < i\text{-C}_3\text{H}_7 < t\text{-C}_4\text{H}_9 < \text{aryl}$.

The results agree with a mechanistic pathway in which C-O bond breaking to form an intermediate oxocarbonium ion is the rate-determining step. This is followed by a rapid uptake of a hydride ion by the oxocarbonium ion.

Some evidence is given to support the view that reduction by the species AlClH_2 does not occur via a four-center transition state or by a SN_2 mechanism.

The proportion of ring cleavage to ring retention depends primarily upon the ability of groups via polar effects to stabilize one of the intermediate

carbonium ions. Steric effects are considered to be relatively unimportant and operate only where polar effects are equal in the two possible routes.

In agreement with this it is found that electron donor substituents at C₆ produce a high proportion of ring retention product, whereas an electron withdrawing group at C₆ gives the reverse result. Electron withdrawing groups such as OCH₃ or Br at C₃, because of their destabilization of the intermediate carbonium ion via polar effects cause a marked reduction in the rate of hydrogenolysis. As well, such groups at C₃ (OH and OCH₃) change the proportion of ring cleavage to ring retention products. This is believed due to neighbouring group participation in promoting cleavage of the C-O bond orientated trans to such a participating group.

The greater rate of hydrogenolysis of the 2-alkoxy-3-hydroxy-tetrahydropyrans compared to that of the 2-alkoxy-3-methoxytetrahydropyran was rationalized in terms of less destabilization of the intermediate carbonium ion due to conversion of the C₃-OH group to the anion by reaction with hydride.

A comparison was made of the rates of hydrogenolysis of C₂ substituted 1,3-dioxolanes and 1,3-dioxanes. It was found that 1,3-dioxolane acetals react faster than do the 1,3-dioxane acetals. The reverse is true of the corresponding ketals. This was explained in terms of two 1,3-diaxial C//H interactions present in the 6-membered ring ketals but not in the 5-membered ring ketals.

The close similarity between the acid catalyzed hydrolysis and

the $\text{AlCl}_3\text{-LiAlH}_4$ hydrogenolysis of acetals and ketals is pointed out.

The possibility is suggested of the use of the hydrogenolysis reaction to trap the intermediate oxocarbonium ions, via rapid hydride addition, and thus gain information concerning the problem of hydrolysis of glycopyranosides. Preliminary experiments on methyl 2,3,4,6-tetra-O-methyl- α -D-glucopyranoside indicate that hydrogenolysis is very slow and occurs only by ring cleavage.

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INTRODUCTION

I. OBJECTIVES

The work in this thesis had a four-fold purpose.

a) The study by Leggetter and Brown (1) of the hydrogenolysis of cyclic acetals and ketals of the type I_a and I_b (Chart 1) with the mixed reagent*, clearly showed that substituents R and R' on carbon 2, had a marked

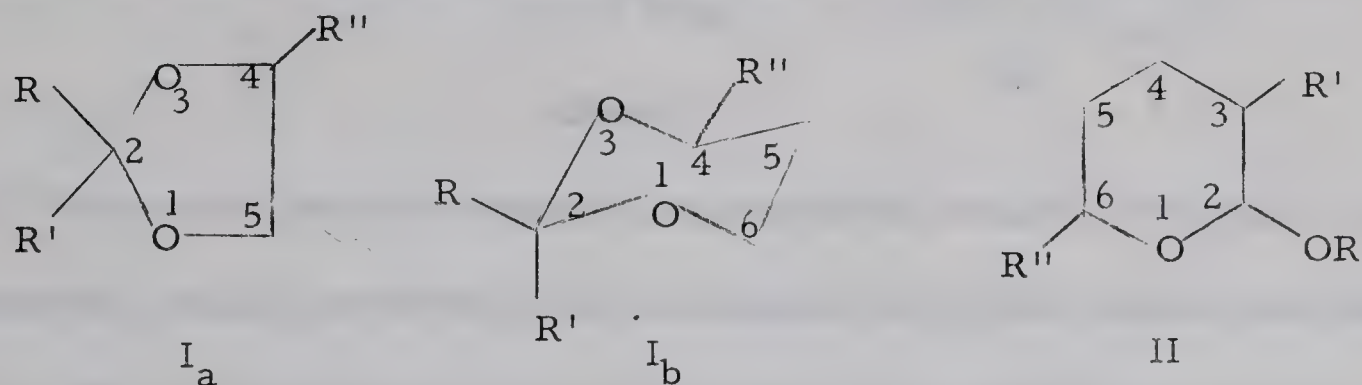


Chart 1

effect on the rate of reduction, whereas substituents R'' on carbon atoms other than C₂ had only a small effect on this rate. However substituents R'' located in the position shown in I_a and I_b , strongly affected the direction of ring cleavage. Two isomeric products were obtained from the hydrogenolysis of these cyclic acetals and ketals (Chart 2). The preponderance of one isomer over the other as well as the rate of ring cleavage was rationalized in terms of the polar character of the substituents.

The present work continued these studies on the acetals which contain the 2-alkoxytetrahydropyran ring structure II (Chart 1).

* The mixed reagent is understood to be mixtures of LiAlH_4 and AlCl_3 . The ratios that have been used are $\text{LiAlH}_4:\text{AlCl}_3$ 3 to 1, 1 to 1 and 1 to 3, as well as 1:4.

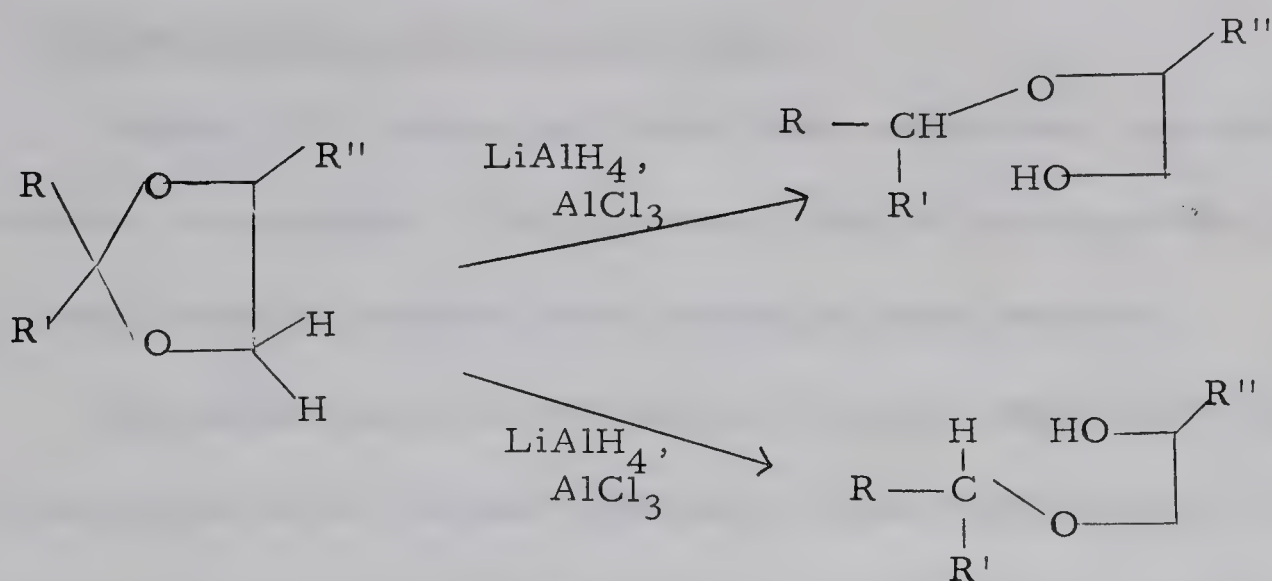


Chart 2

- b) The second objective was to determine the nature of the reducing species actually involved in the hydrogenolysis of the acetals and ketals when the hydrogenolysis was carried out by the method employed by Leggetter and Brown (1). This information was considered essential for the development of a reasonable mechanism of hydrogenolysis.
- c) The third objective was to obtain suitably substituted 2-alkoxy-tetrahydropyrans (II, Chart 1) which could be used as simple homologues of glycopyranosides. These could then be hydrogenolyzed with the mixed reagent to discover the influence of substituents on the extent of ring cleavage versus side chain cleavage.
- d) The fourth objective was to hydrogenolyze simple glycosides, applying the knowledge gained in objectives (a) and (c) to explain and/or predict the results obtained. It was hoped that the results of hydrogenolysis might throw some light on the problem of hydrolysis of the glycopyranosides.

II. LITERATURE SURVEY

A. Hydrogenolysis of Acetals and Ketals

Before 1951 acetals and ketals were reductively cleaved by essentially two methods. The first was catalytic hydrogenation and the second involved reduction with metals in liquid ammonia.

Hydrogen over a nickel catalyst (2) gave complete hydrogenation with conversion of the carbonyl substance to the hydrocarbon, and formation of the original alcohol (Chart 3, equation a). In a few instances only was cleavage of just one of the oxygen-carbon bonds obtained, but the resulting compound was invariably just one member of a mixture of products (Chart 3, equation b).

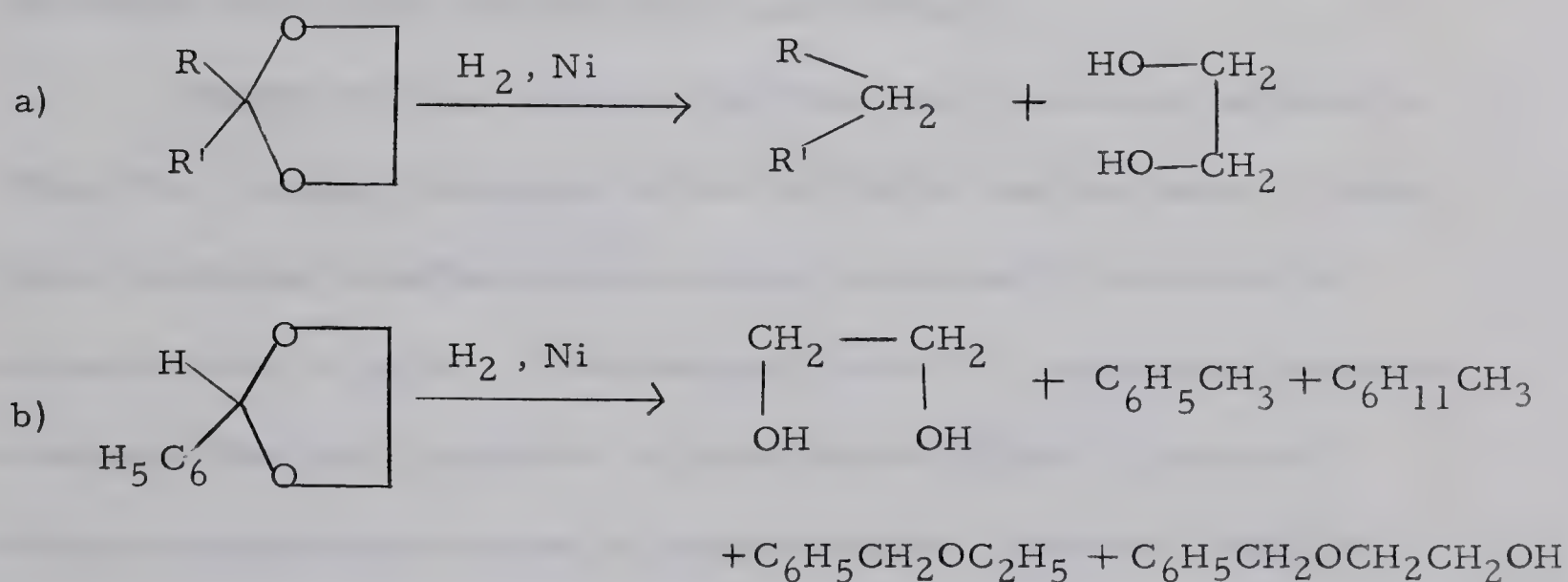


Chart 3

Howard and Brown (3) using hydrogen in the presence of a rhodium catalyst in acid medium were able to obtain selective cleavage. They suggested that their results could be explained by a mechanism that involved carbonium ion formation (Chart 4).

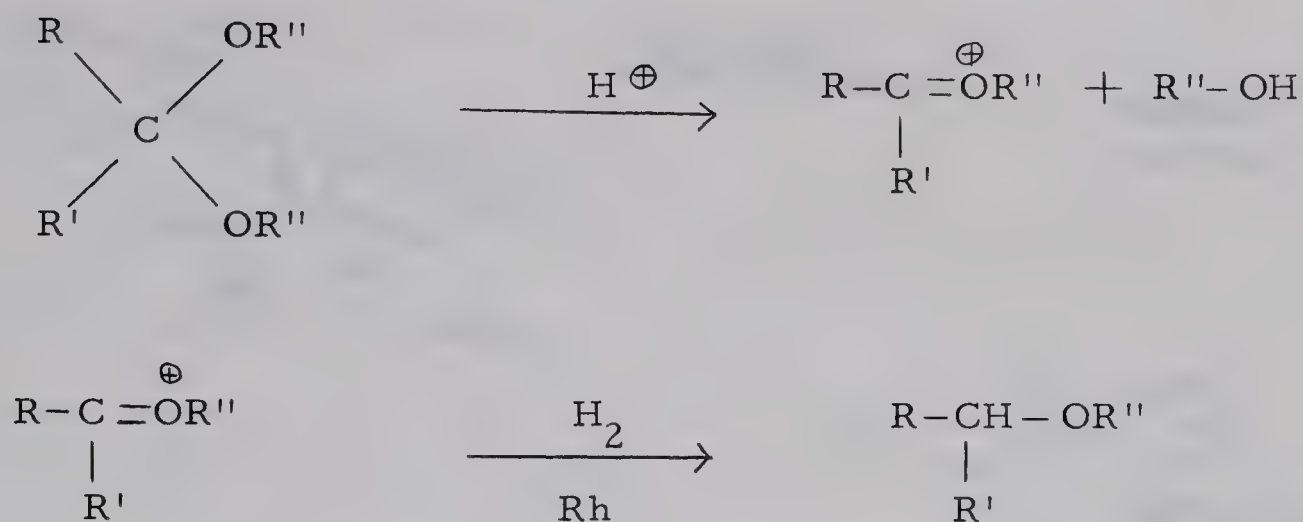


Chart 4

There was no distinct advantage of this method over the one previously mentioned, because the yields were generally poor ($\sim 25\%$) and some undesirable products were also formed.

Sodium in liquid ammonia has been used by several authors to effect the cleavage of oxygen-carbon and sulfur-carbon bonds. Under these conditions thioethers were reduced more easily than were the oxygen ethers (4, 5, 6). Jamieson and Brown (7) reported the reductive cleavage of methyl S-benzyl-4,6-O-benzylidene-2-(or -3)-thio- α -D-altropyranosides with sodium in liquid ammonia. The only isolable compounds were the unchanged starting material and 2- or 3-thioglycoside with both protecting groups removed (Chart 5).

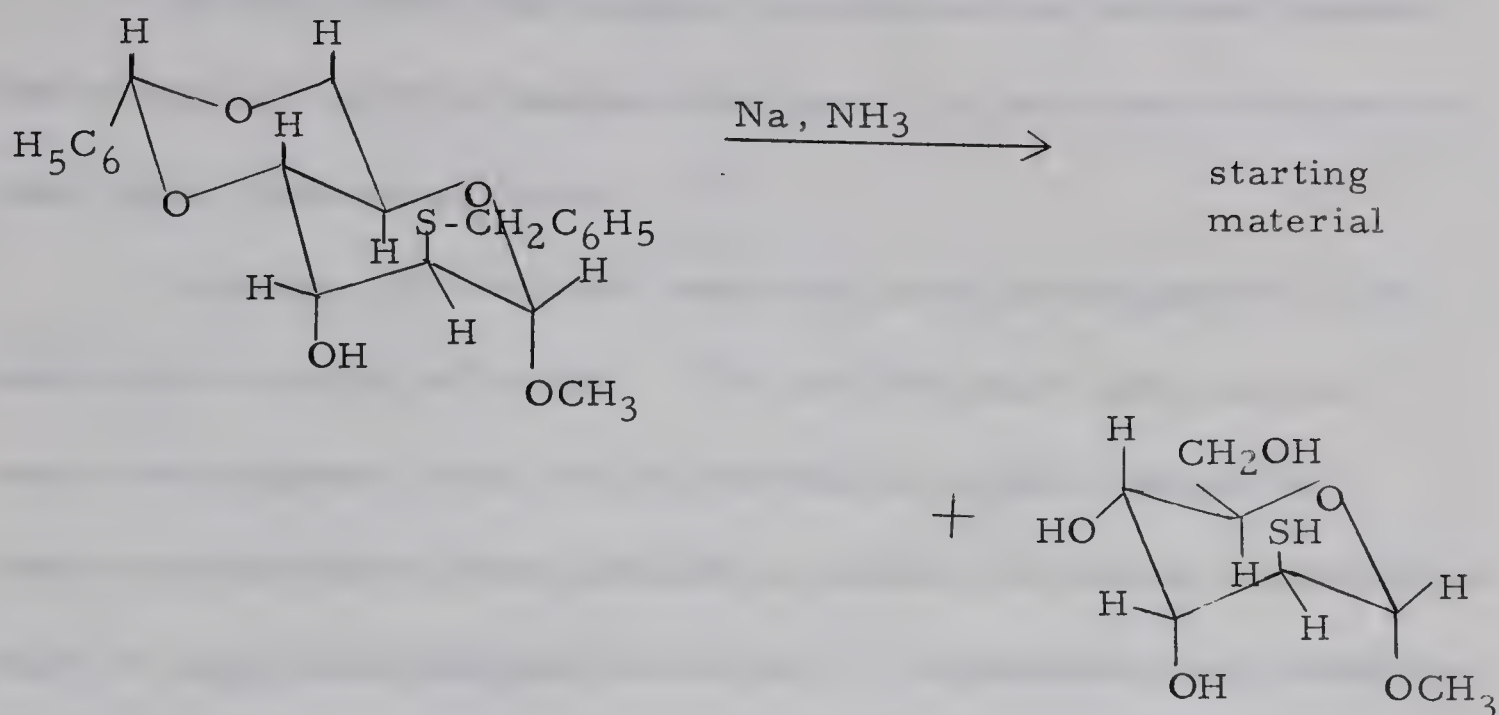


Chart 5

Later in 1966, Nayak and Brown (8) reported that selective cleavage of the C-S bond could be obtained by using 1,2-dimethoxyethane as a co-solvent with the liquid ammonia (Chart 6).

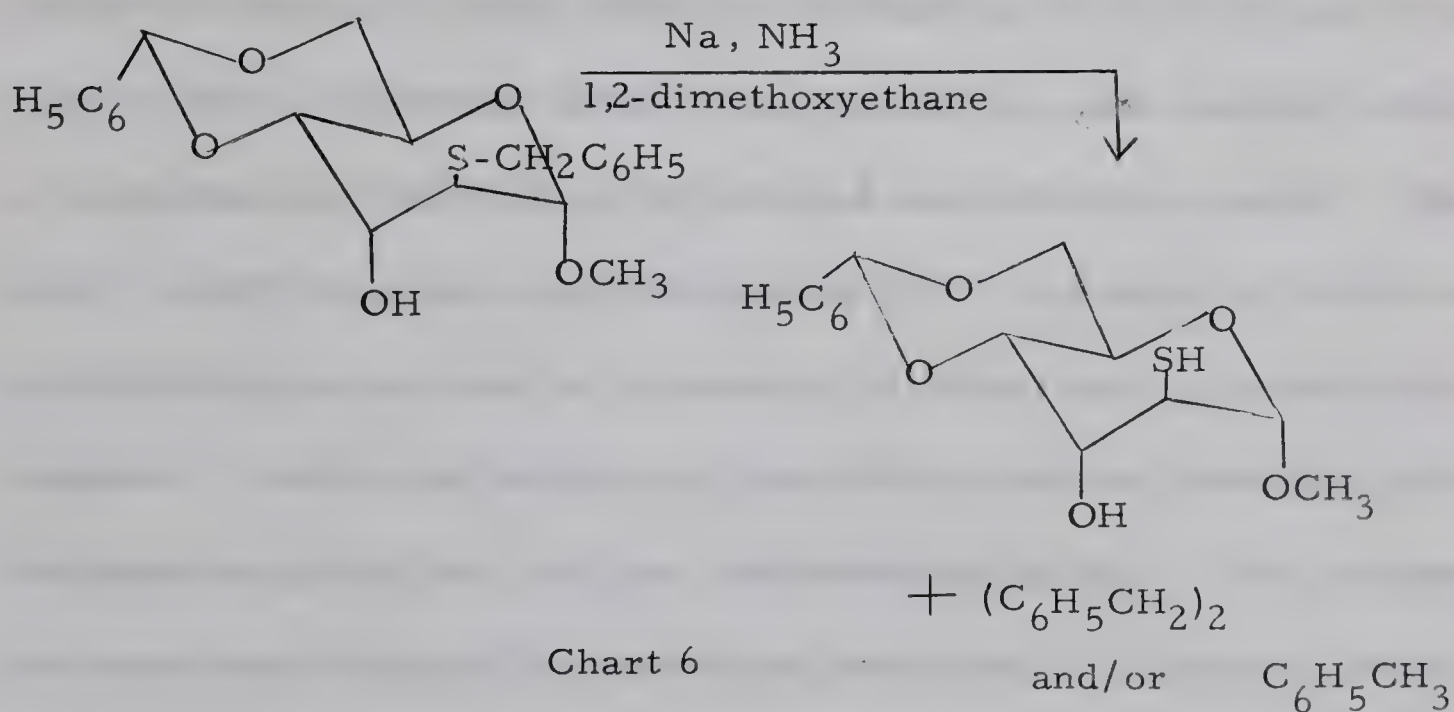


Chart 6

Sodium in liquid ammonia was used by Pinder and Smith (9) to reduce 2-methyl-2-phenyl-1,3-dioxolane and 2-methyl-2-phenyl-1,3-oxathiolane.

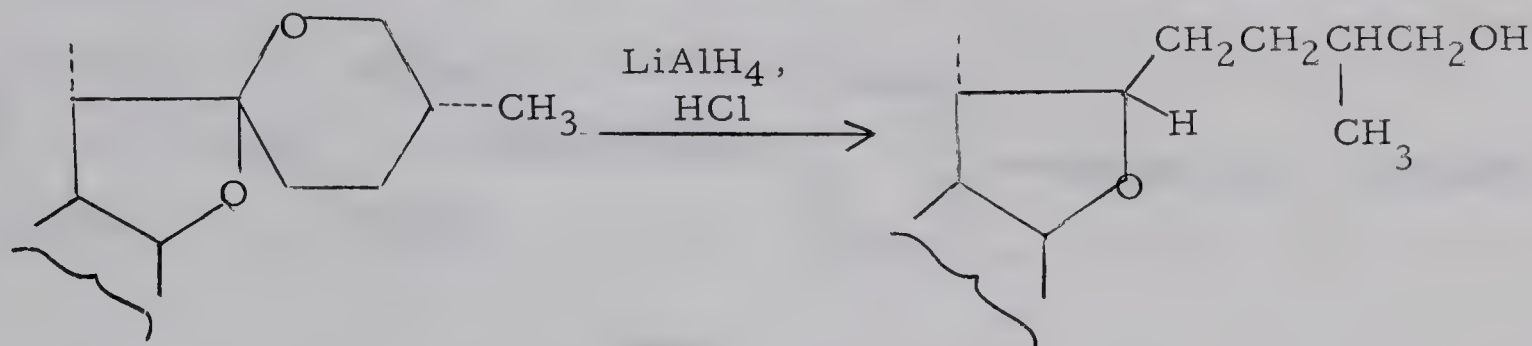
In both cases ethylbenzene was obtained as the main product, with traces of 1-ethylcyclohexa-1,4-diene. No selective cleavage was observed in these experiments.

Recently hydrides have been used quite advantageously in the reduction of acetals and ketals. The last few years have seen an intense development of the use of hydrides in organic chemistry. Reductions that before were difficult to achieve can now be accomplished easily in high yields and quite selectively. An excellent and extensive review of the use of hydrides has been made by Gaylord (10). Rerick (11) and Eliel (12) have reviewed reductions brought about by combinations of LiAlH_4 and AlCl_3 .

LiAlH_4 is one of the best known double hydrides and has been in use for almost 20 years since its introduction by Nystrom and Brown (13) in 1947. A number of functional groups (e.g. the carbonyl groups of aldehydes and ketones) can be reduced easily by this reagent. However, LiAlH_4 does not react with ethers (10). Accordingly, ether and tetrahydrofuran are used as solvents to carry out reductions with this reagent. Acetals and ketals are geminal diethers and therefore it is not surprising that they are also unaffected by LiAlH_4 . This property has been useful since it has permitted protection of a carbonyl group from hydride reduction by its prior conversion to an acetal or ketal (10).

However, the addition of an acid to the reducing system changes this picture drastically. In 1953, Doukas and Fontaine (14) successfully

reduced spirostanols to furostanols by the action of solid LiAlH_4 on an ethereal solution of the spirostanol saturated with HCl or HBr .



Acids other than HCl or HBr were not effective. Apparently the presence of an acid here was essential to bring about the reduction. Under the conditions employed, the direction of cleavage was quite specific. Since the only acids effective in promoting the reduction of spirostanols to furostanols were HCl or HBr (14), Eliel and Rerick(15) proposed that $\text{LiAlH}_4/\text{AlCl}_3$ was actually the active reagent in the experiment carried out by Doukas and Fontaine, the AlCl_3 being formed in situ by the action of the HCl upon the LiAlH_4 .

After the work of Doukas and Fontaine had appeared a number of Lewis acids have been used with LiAlH_4 to increase the selectivity in the reducing properties of this reagent, but the one most commonly employed is AlCl_3 . The term "mixed reagent" has been used to designate mixtures of LiAlH_4 and AlCl_3 . The mixture most commonly used is one in which LiAlH_4 and AlCl_3 are present in the ratio of 1:4. Other ratios frequently used are $\text{LiAlH}_4:\text{AlCl}_3 = 3:1$ or 1:1. In 1958, Eliel and Rerick(15) studied the reduction of some acetals and ketals with the combination of $\text{LiAlH}_4/\text{AlCl}_3$ present in a 1:4 ratio. It was found

that acetals and ketals were hydrogenolyzed by the mixed reagent to the corresponding ether, as shown in Chart 7.

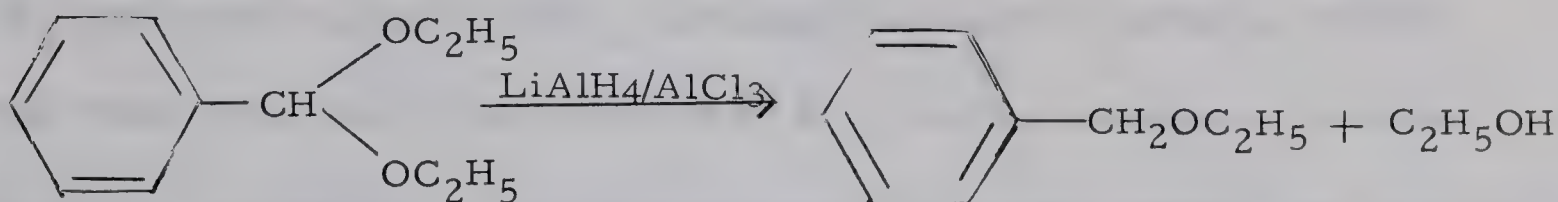


Chart 7

Three years later, Eliel (12) published a review of the action of the mixture AlCl₃-LiAlH₄ (in a 4:1 ratio) on a variety of substances, including acetals, ketals, hemithioacetals, hemithioketals, epoxides and ketones.

Mixed hydride reduction was later (16) extended to cyclic acetals and ketals. In 1962, Eliel et al (17) also studied the hydrogenolysis of the two isomers of the 4-t-butylcyclohexanone ethylene hemithioacetal with LiAlH₄ / AlCl₃ and with combinations of BF₃ and LiAlH₄ (Chart 8).

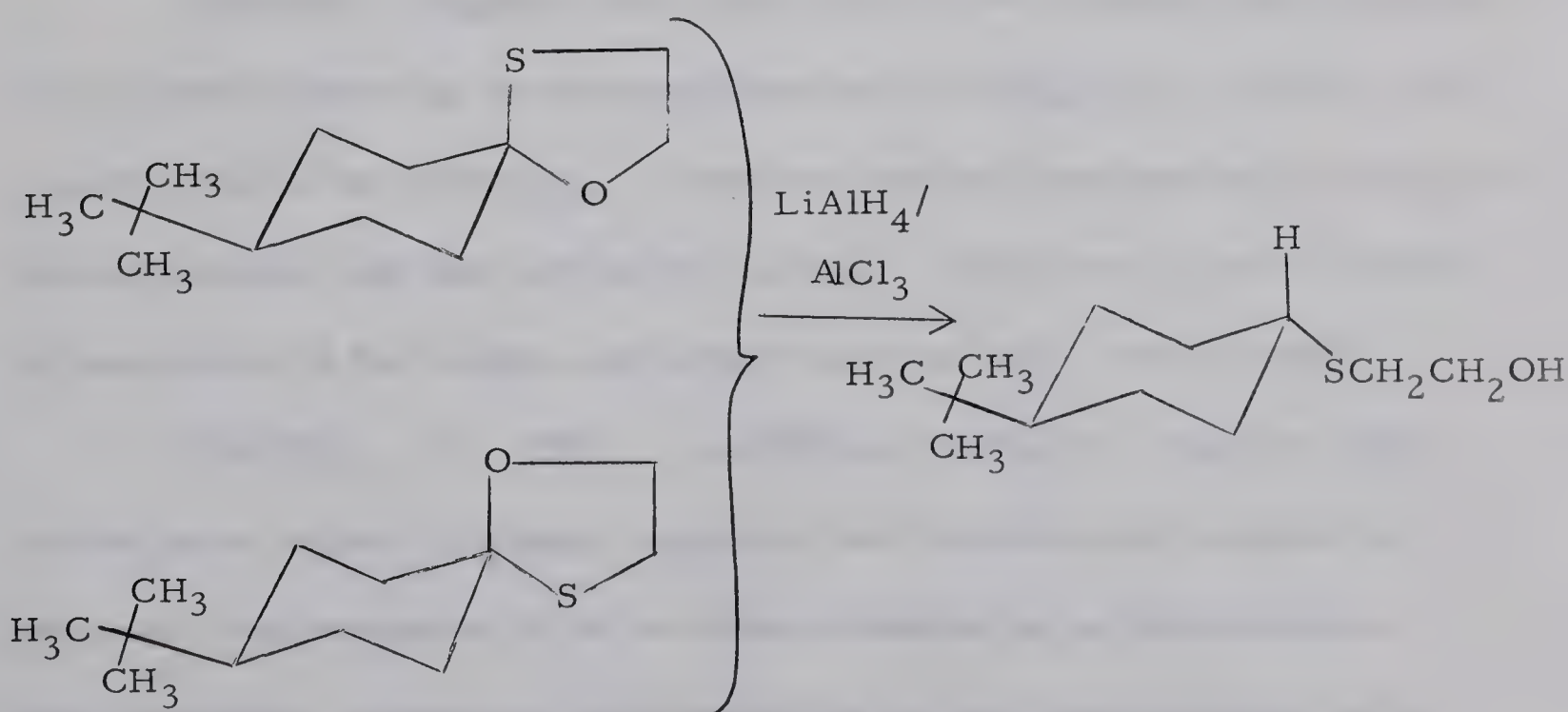
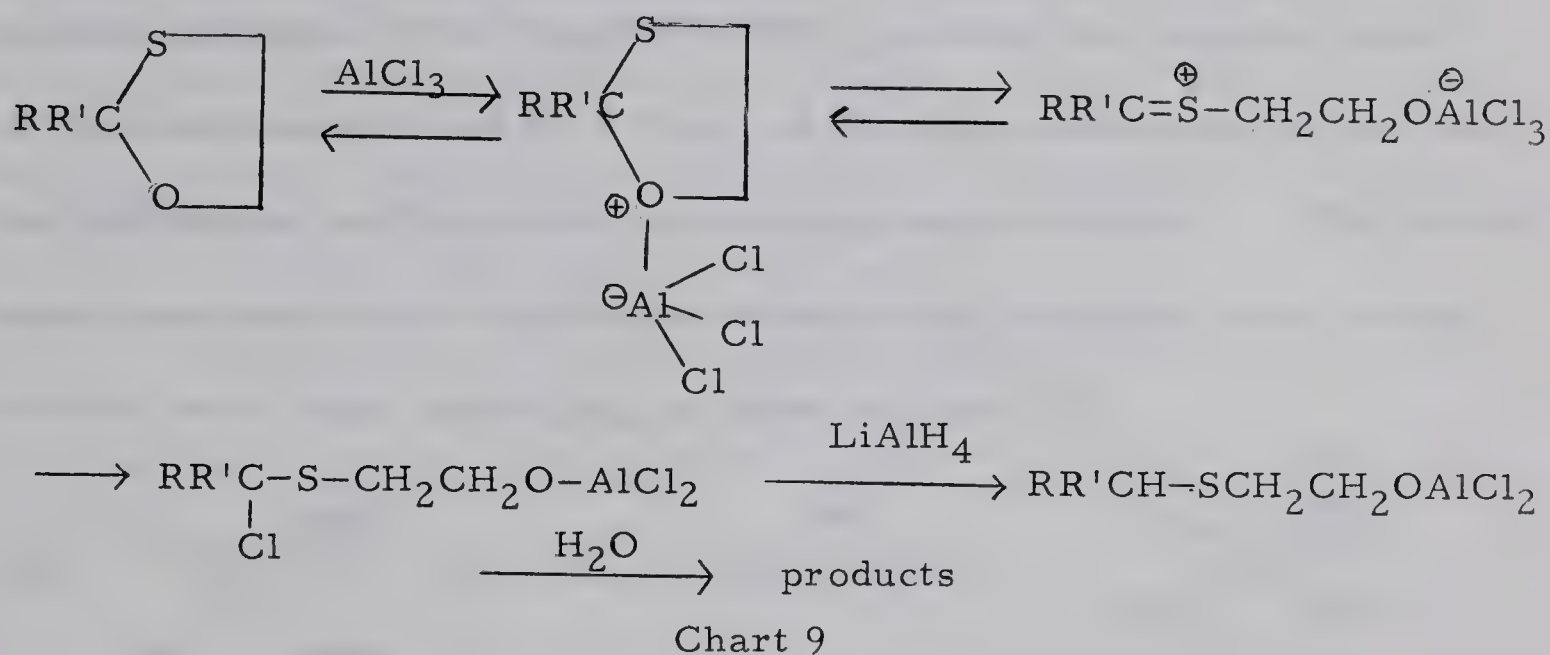


Chart 8

It was found that the two isomers produced the same thioether, the trans isomer, as shown in Chart 8. No reduction was observed if BF_3 was used in place of AlCl_3 , although the diastereoisomeric mixture was found to be readily equilibrated by BF_3 in ether solution. On these grounds a mechanism of hydrogenolysis by the mixed reagent was proposed which involved the formation of an α -chloro thioether as an intermediate (Chart 9).

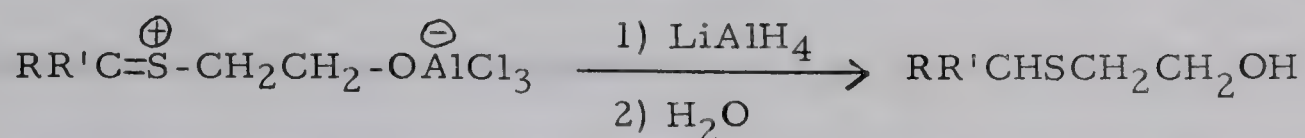


However, Leggetter and Brown (18) in 1963 showed that reduction of 1,3-oxathiolanes can be accomplished with $\text{LiAlH}_4/\text{BF}_3$, contrary to the results obtained by Eliel et al. This was done by first mixing the BF_3 and the oxathiolane, and then adding the LiAlH_4 . In this way, loss of hydride by conversion to the volatile and ether-insoluble B_2H_6 , was avoided.



On the basis of their findings, Leggetter and Brown do not consider as necessary the formation of the α -chloro thioether as an intermediate. They postulate instead the direct reduction of the thiocarbonium ion by

the hydride present, as illustrated below.



In 1964 Leggetter and Brown (1) pointed out the striking similarity between the results of the reductive cleavage of acetals and ketals and the rates of acid-catalyzed hydrolysis of substituted acetals. It had been shown by Kreevoy and Taft (19, 20) that the rate of hydrolysis of acetals and ketals of the type $\text{RR}'\text{C}(\text{OR}'')_2$ parallel the inductive order of the substituents R and R'. Electron donating substituents accelerated the hydrolysis, while electron attracting groups retarded it. The results were consistent with a mechanism in which the formation of an oxocar-bonium ion is rate controlling as shown in Chart 10.

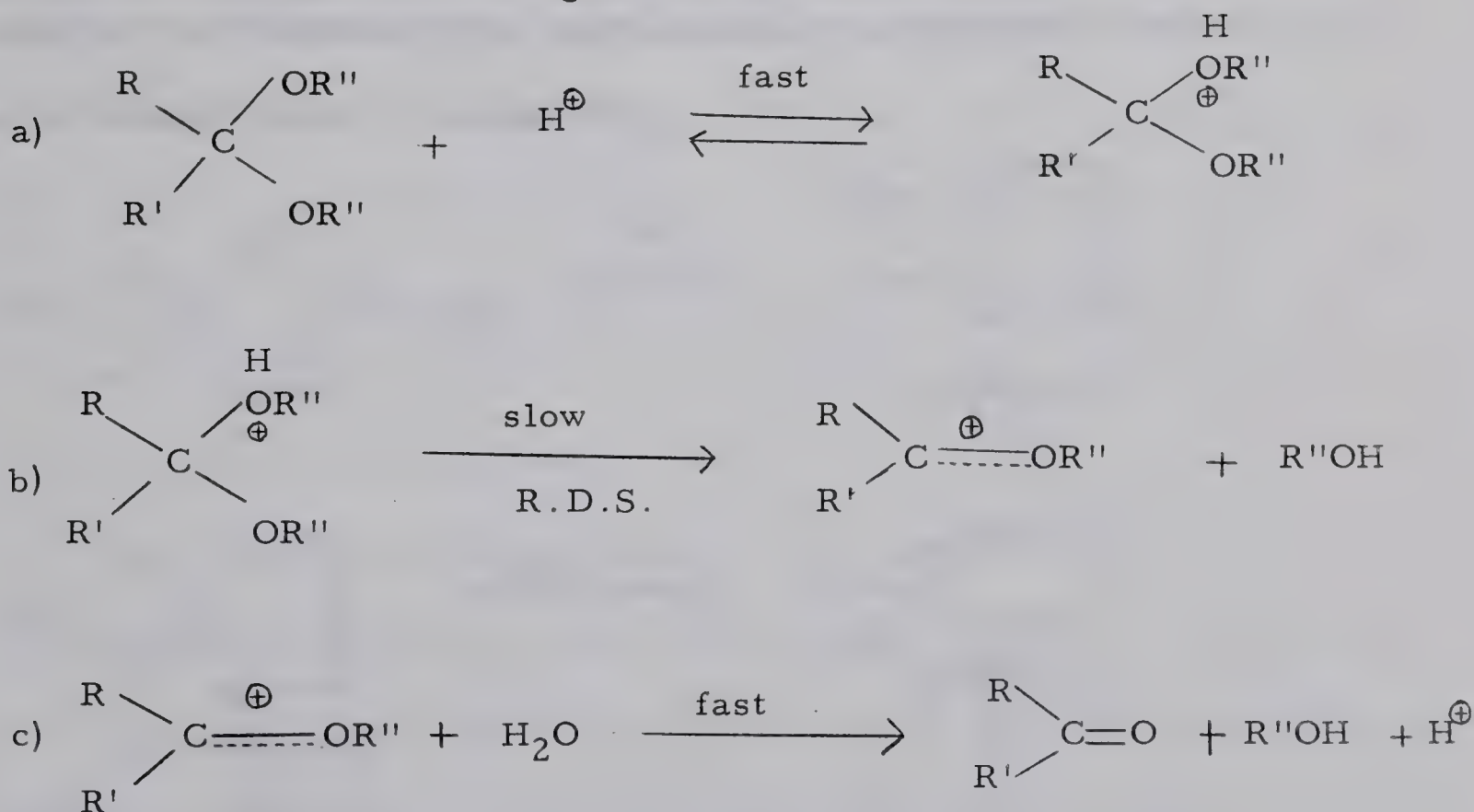


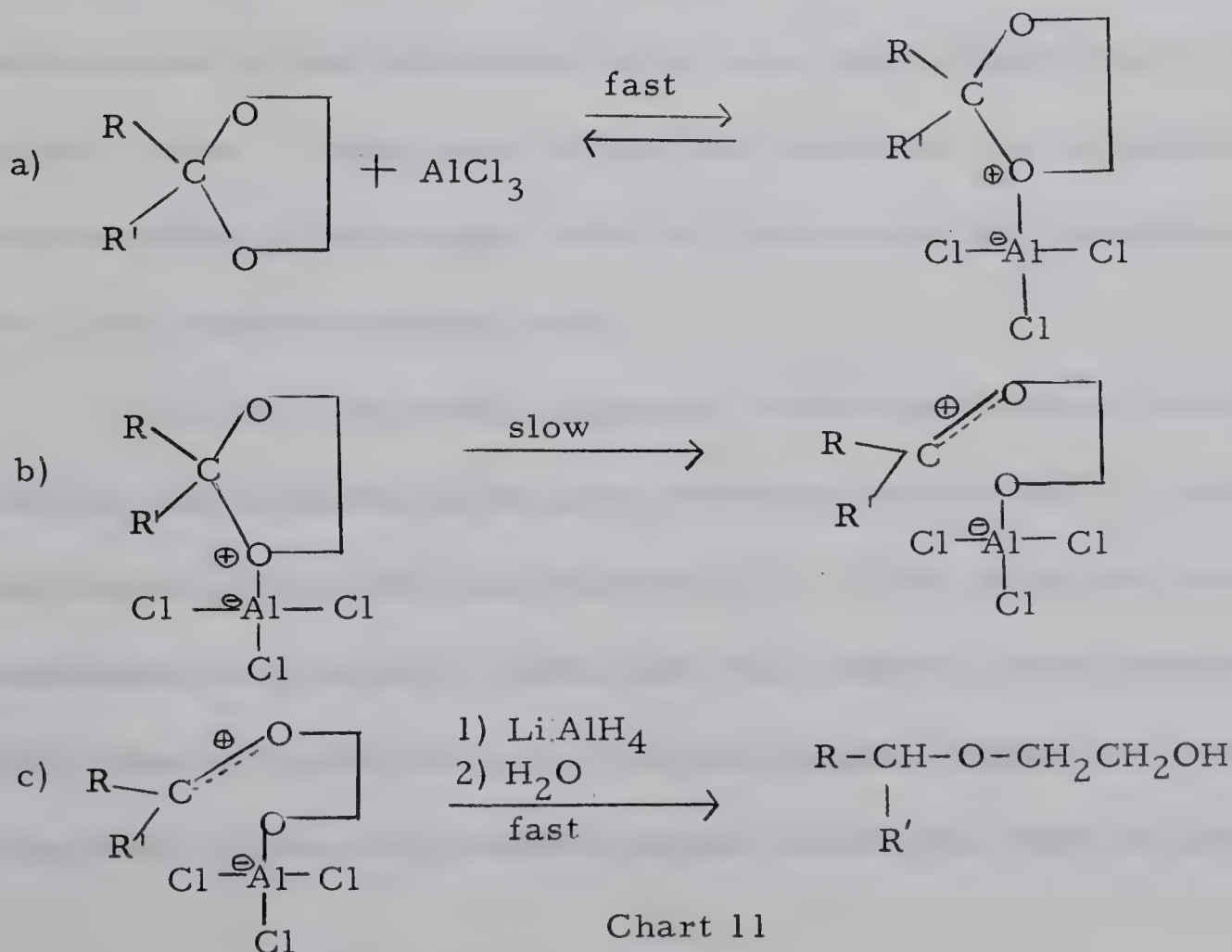
Chart 10

Any substituent, R and R', which could stabilize the oxocarbonium ion would thus enhance the rate of hydrolysis.

A similar mechanistic view was postulated by Leggetter and Brown (1) concerning the hydrogenolysis of ketals and acetals.

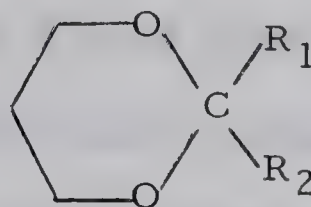
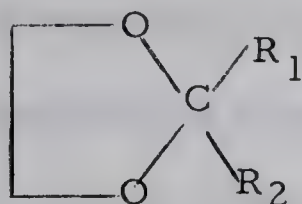
They found that electron donor substituents on the C₂ atom of the dioxolane ring accelerate the rate of hydrogenolysis while electron withdrawing groups on the same carbon retard the reaction rate. Also, electron donor substituents attached to C₄ promote preferential cleavage of the C₂-O bond remote from the C₄ position. The reverse is true for electron attracting substituents attached to C₄.

According to these findings they proposed (1) a fast reversible step that corresponds to the coordination of the substrate with the Lewis acid present (Chart 11, equation a).



Then the formation of an oxocarbonium ion takes place and this is believed to be the rate-determining step (Chart 11, equation b). Groups R and R' which stabilize the oxocarbonium ion would enhance the rate of its formation and hence the rate of hydrolysis. The carbonium ion is then rapidly and irreversibly reduced as shown in equation c.

In 1932, Leutner (21-24) studied the acid-catalyzed hydrolysis of alkylated 1,3-dioxolanes and 1,3-dioxanes. In 1954, Ceder (25) studied the hydrolysis of cyclic acetals such as the following:



where R₁ and/or R₂ are aryl groups. Both, Leutner and Ceder found that where R₁ and R₂ are substituents which are able to stabilize a positive charge, the hydrolysis takes place more readily than in the contrary case. Ceder also favored the carbonium ion mechanism for the hydrolysis of the acetals, with the formation of the oxocarbonium ion as the rate-determining step.

Recently a report has appeared concerning a kinetic study at different temperatures of the acid-catalyzed hydrolysis of 1,3-dioxolanes and several of its methyl derivatives (26). It was found that one methyl substituent at C₂ of the 1,3-dioxolane ring caused a great increase ($\sim 10^3$) in the speed of hydrolysis. An increase in rate of hydrolysis was also observed, but to a much smaller degree (about 10%) when an alkyl group

was attached to C₄. An introduction of a second methyl group at C₂ lead to a further increase in the rate of hydrolysis, but this was considerably less pronounced than that observed for the introduction of the first methyl group. This phenomenon was explained on the basis of steric considerations. They found that their results could be explained by a mechanism which agreed with that postulated by Ceder; a slow rate determining step that follows the rapid proton uptake by the dioxolane.

While the work for this thesis was in progress, Eliel et al (27) reported the study of the hydrogenolysis of some tetrahydropyranyl ethers. They obtained both ring cleavage and side chain cleavage, the relative proportion of which depended on the substituent R (Chart 12).

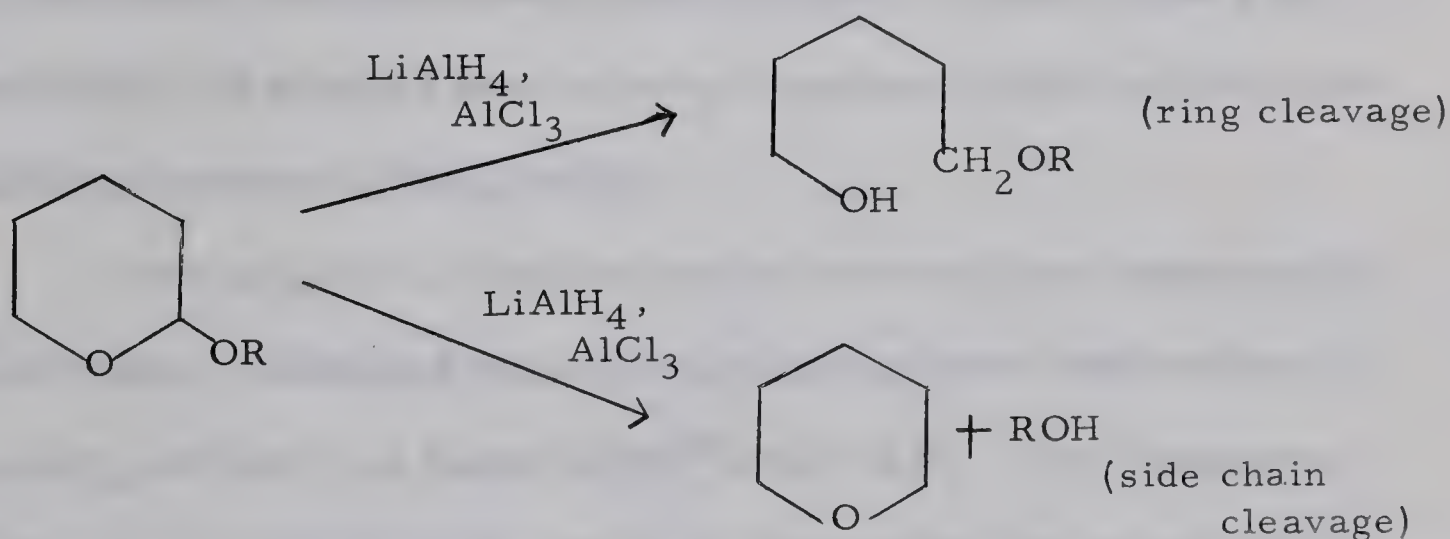


Chart 12

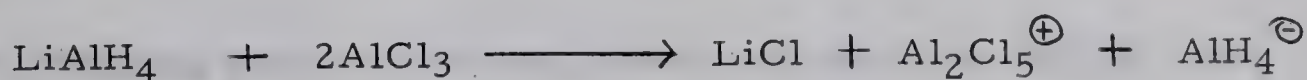
They found that when R is a tertiary alkyl group, ring cleavage is favored, while a primary alkyl group, R, promotes side chain cleavage. These results were explicable in terms of polar factors, since tertiary alkyl groups are better electron donors than are primary alkyl groups. They also pointed out that the preference for ring cleavage when R is a

tertiary group, could be explained on steric grounds. The bulk of the tertiary alkyl group would make coordination of the Lewis acid with the exo oxygen more difficult, hence preferential coordination of the Lewis acid with the ring oxygen atom would take place with consequent ring cleavage. It was felt that both polar and steric factors could thus be involved.

B. The Nature of the Reducing Species Obtained from the Mixture of AlCl_3 and LiAlH_4 .

In 1947, Finholt et al (28) found that the reaction of three moles of LiAlH_4 with one of AlCl_3 in ether gave solutions of AlH_3 which were quite unstable. There was a strong tendency for the AlH_3 to polymerize when its ethereal solution was allowed to stand. Later, Wiberg and Schmidt (29, 30) obtained from an ether solution of AlH_3 and AlCl_3 the distillable substance $\text{AlHCl}_2 \cdot \text{AlH}_2\text{Cl}$.

Evans et al (31), from the results obtained from conductivity measurements, postulated the species resulting from combinations of the LiAlH_4 and AlCl_3 as being Al_2Cl_5^+ and AlH_4^- . They suggested the following stoichiometry for the initial step of the reaction between LiAlH_4 and AlCl_3 .



In a recent publication (32) Ashby and Prather showed quite clearly that the reducing agent obtained from a mixture of AlCl_3 and LiAlH_4 in ether is AlH_3 , AlClH_2 or AlCl_2H depending upon whether the

molar proportion of AlCl_3 to LiAlH_4 is 1:3, 1:1 or 3:1. They also showed that each of the species showed a characteristic infrared absorption due to Al-H stretching. This characteristic absorption was obtained from benzene solutions of complexes of each species with either triethylamine or diethyl ether. In this way each species could be readily identified in solution.

The existence of species such as AlCl_2H was foreseen by Eliel in 1961 (12) who also suggested the possibility of a complex being formed between the LiCl and the AlCl_2H . These facts were actually demonstrated by Ashby and Prather. Included in the paper by the latter authors was the mode of action of the mixed reagent on epoxides. Following Eliel's work on the hydrogenolysis of epoxides (33), Ashby and Prather suggested the possible formation of a four centre transition state (Chart 13) when the reducing species is a weak Lewis acid.

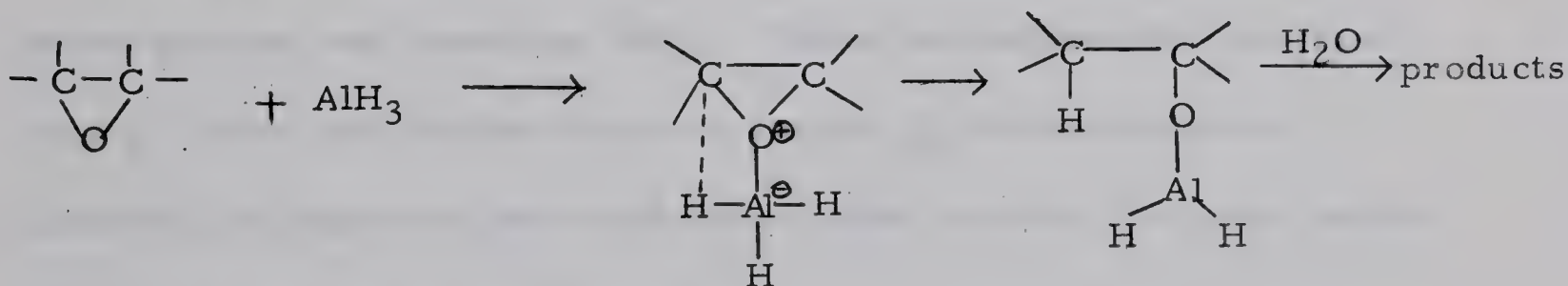


Chart 13

four centre transition
state

But if the attacking agent is a strong Lewis acid such as AlCl_2H , they believe that the mechanism of reduction involving the formation of a carbonium ion is operative (Chart 14).

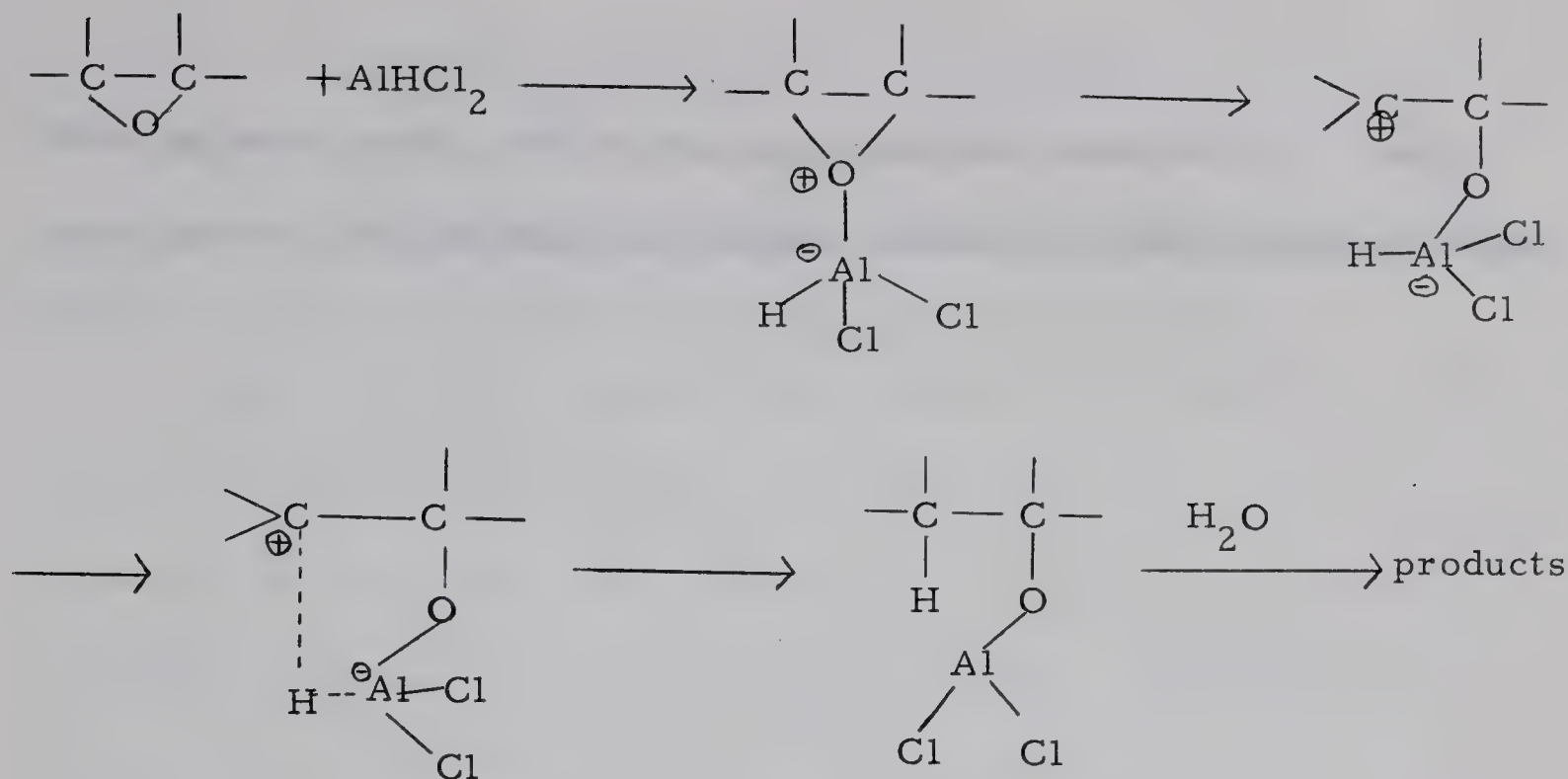


Chart 14

In these mechanisms the transfer of the hydride was considered to be intramolecular.

Lansbury and Pattison (34) in 1966, studied the action of the mixed reagent on epoxides using a $\text{LiAlH}_4/\text{AlCl}_3$ ratio of 3/1. The active species was therefore AlH_3 . While the mechanistic interpretation of Ashby and Prather involves overall cis stereochemistry, Lansbury and Pattison found that the reaction actually proceeds mainly via trans stereochemistry (Chart 15).

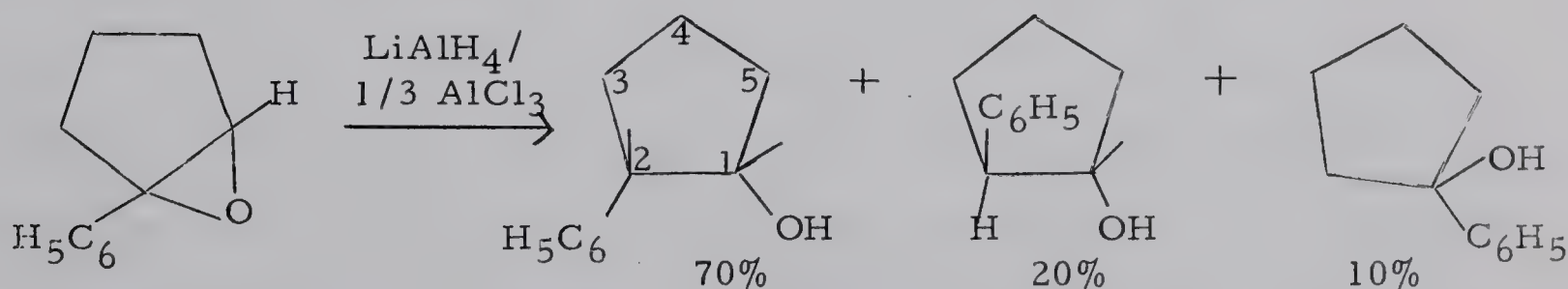


Chart 15

Working with LiAlD_4 , 80% of the deuterium was found at C_2 . These facts seem to indicate that the hydride transfer is mainly intermolecular.

RESULTS AND DISCUSSION

I. The Active Reducing Species in the Reductions Accomplished by the Addition of AlCl_3 to a Mixture of LiAlH_4 and Acetal or Ketal.

Most of the hydrogenolysis experiments described in this thesis and all of those previously reported from this laboratory, were done by the procedure of addition of an ether solution of the Lewis acid (AlCl_3) to a mixture of acetal or ketal and LiAlH_4 in ether. This method has given eminently satisfactory results, hence its general adoption in our work. However, we were not certain of the reducing species actually operative under these conditions.

It was the work recently reported by Ashby and Prather (32) that supplied the information which permitted a study of this point.

A. Interconversion of the Species AlH_3 , AlClH_2 and AlHCl_2 .

Since Ashby and Prather found that the species obtained from a mixture of AlCl_3 and LiAlH_4 is actually AlH_3 , AlClH_2 or AlCl_2H , depending upon whether the molar proportion of AlCl_3 to LiAlH_4 is 1:3, 1:1 or 3:1, it was necessary to know how readily one species can be converted to another, since in our procedure the AlCl_3 is added over a period of time to the mixture of LiAlH_4 and acetal, all reagents in equimolar proportions. It is of interest at this point to mention that Eliel (12) has stated that "the addition of a Lewis acid weakens the nucleophilic character of LiAlH_4 , and while it simultaneously increases the electrophilic

properties of the reagent, the overall effect is usually one of producing lowered reducing power". This can be rationalized knowing the constitution of the reagent produced. The species formed are AlH_3 , AlClH_2 , or AlCl_2H according to the ratio of $\text{LiAlH}_4/\text{AlCl}_3$ used. Each of the species has Lewis acid properties due to the vacant orbital on the aluminum atom. Due to the inductive effect of the chlorine atoms, this electrophilic character is enhanced as we go from AlH_3 to AlCl_2H . On the contrary, this situation is not observed in LiAlH_4 by itself. Its electrophilic character is indeed negligible (34), but it is a better hydride donor than any of the species mentioned and hence has high nucleophilic character.

The following details from the work of Ashby and Prather should also be noted here. In their experiments, LiAlH_4 in ether was added to a solution of AlCl_3 in ether. Their addition of triethylamine to the reaction mixture caused the hydrides to form an adduct with the amine, with consequent precipitation of the LiCl . After evaporation of the solvents this adduct was extracted with benzene and the infrared spectrum taken of this benzene solution of the hydride-amine complex. It was observed that the Al-H stretching band had the following definite values for each of the hydrides: 5.27μ for the $\text{AlCl}_2\text{H} \cdot \text{N}(\text{C}_2\text{H}_5)_3$, 5.40μ for the $\text{AlClH}_2 \cdot \text{N}(\text{C}_2\text{H}_5)_3$, and 5.6μ for the $\text{AlH}_3\text{N}(\text{C}_2\text{H}_5)_3$. They also found that the infrared absorption for the corresponding hydride-ether complexes in benzene were practically the same as those found above. For example,

for $\text{AlCl}_2\text{H} \cdot \text{O}(\text{C}_2\text{H}_5)_2$ the absorption reported was at 5.22μ . The data for the other hydrides were not given.

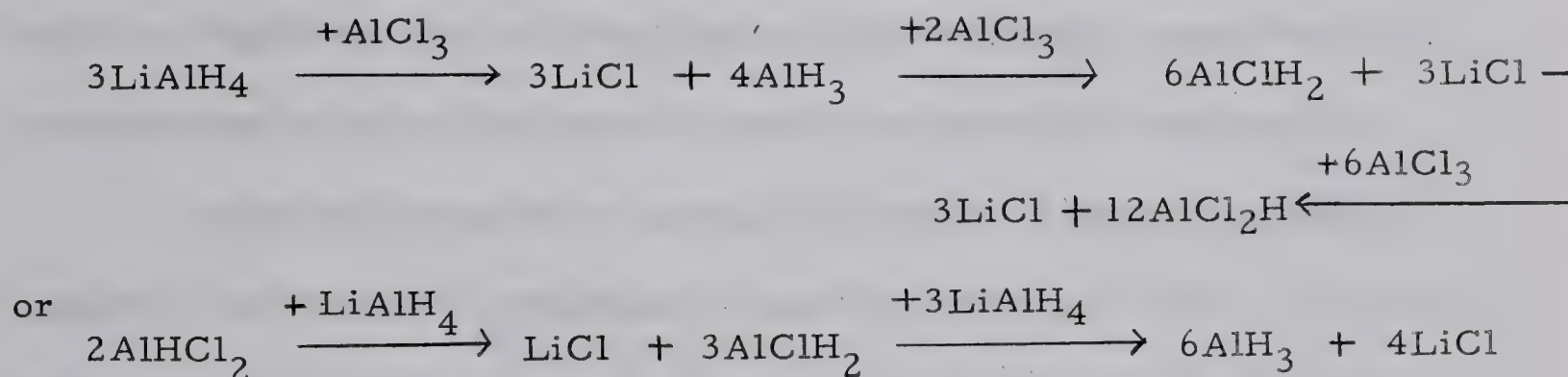
We prepared an ether solution of each species by the addition of the Lewis acid, AlCl_3 , in ether, to the LiAlH_4 also in ether. The infrared spectra of the reaction mixtures were obtained, and showed the Al-H absorption bands to be at: 5.75μ for LiAlH_4 , 5.23μ for AlCl_2H , 5.39μ for AlClH_2 and 5.59μ for AlH_3 . These values were quite similar to those obtained by Ashby and Prather. We did not observe the precipitation of LiCl except in the case when AlH_3 was prepared and the solution was left standing for a few minutes:

When AlCl_3 in ether was added to an ether solution of LiAlH_4 and the ratio of the halide to LiAlH_4 was 1:3, the infrared absorption of the supernatant liquid showed a strong band at 5.59μ , indicative of the species AlH_3 . If more AlCl_3 was added to this solution to give a final ratio of AlCl_3 to LiAlH_4 of 1:1, the band at 5.59μ was replaced by one at 5.39μ showing that the AlH_3 was replaced by AlClH_2 . Furthermore, if enough AlCl_3 was added to give a ratio of $\text{AlCl}_3/\text{LiAlH}_4$ of 3:1, again only one band was observed, a strong one at 5.23μ , showing AlCl_2H as the only species present.

We were able to convert AlCl_2H to AlH_3 quite readily by addition of the proper amount of a solution of LiAlH_4 to the ethereal solution of AlClH_2 . The resulting solution showed only one band, a strong one at 5.59μ , characteristic of AlH_3 .

It was shown also that two species can be present in solution simultaneously. This was done by adding an amount of AlCl_3 to a solution of AlH_3 sufficient to convert only a part of it to AlClH_2 . In this case two maxima were observed, one at 5.4μ and the other at 5.6μ , corresponding to AlClH_2 and AlH_3 respectively.

It is clear from the work described above that it is possible to convert one species to another in a reversible fashion by the addition of the proper amounts of LiAlH_4 or AlCl_3 . The conversion occurs quite rapidly and it is complete within three minutes. This was the time required to mix the solutions and take the I.R. spectrum. The following equations illustrate the stoichiometric sequence of the changes.



In our experiments on hydrogenolysis, as in those reported by Leggetter and Brown (1), we began with a solution containing the acetal and LiAlH_4 . The addition of AlCl_3 to this solution first gave the species AlH_3 . This was the only species present when the AlCl_3 had been added to the extent of one third. The LiCl did not precipitate, possibly due to the fast addition of AlCl_3 . As further addition of AlCl_3 occurred, the AlH_3 was converted to AlClH_2 , which gave a stable complex with LiCl .

AlClH_2 was the final species present in solution, according to the proportions of reagent used.

B. The Relative Reducing Ability of AlH_3 , AlClH_2 and AlCl_2H and the Nature of the Reducing Species Obtained in Our Hydrogenolysis Procedure.

Experiments were performed to assess the relative reducing ability of the three reducing species. They were prepared by addition of an ether solution of AlCl_3 to one of LiAlH_4 in the proportion required to give the necessary species. To this solution was then added an appropriately chosen acetal or ketal. The results are shown in Table I. These experiments not only showed the relative reducing ability of each of the species, but also provided the necessary information which permitted a decision regarding the reducing species involved in the experiments on hydrogenolysis, using the addition procedure generally employed (1).

When the reduction of acetals and ketals is done according to Leggetter and Brown's procedure (1) and the addition of AlCl_3 is rapid (three minutes or less), since the formation of the species is a fast process, the AlH_3 formed initially could bring about reduction for a period of about one minute only. With reactive acetals, such as 2-phenyl-1,3-dioxane (Table I, expt. 11) the extent of reduction with AlH_3 (the AlH_3 and acetal being in equimolar proportions) is only 9% in 15 minutes. Since by following Leggetter and Brown's procedure (1) AlH_3 is present for about one minute, we see that the extent of reduction due to this species is quite small (about 1%). With less reactive acetals such as 4-methyl-1,3-dioxolane,

TABLE I

Comparison of the Reducing Abilities of AlH_3 , AlClH_2 and AlCl_2H .

Compound	Expt. No.	Reducing Agent	Reduction Time, min.	Extent of Reduction, %	Recovery of Material, %	Hydrogenolysis Products ^f	
						Primary Alcohol, %	Secondary Alcohol, %
2,2,4-trimethyl-1,3-dioxane	1	AlH_3^a	30	98	75	80	20
	2	AlH_3^a	15	64	75	80	20
	3	AlClH_2^a	15	98	75	80	20
4-methyl-1,3-dioxolane	4	AlH_3^a	90	7	75	90	10
	5	AlClH_2^a	90	54	87	90	10
	6	Method in ref. 1 ^b	90	48	78	90	10
	7	AlClH_2^e	90	42	70	90	10
	8	Method in ref. 1	90	45	80	90	10
	9	AlCl_2H^d	90	85	78	90	10
	10	Method in ref. 1 ^c	90	90	75	90	10
2-phenyl-1,3-dioxane	11	AlH_3^a	15	9	80	-	-
	12	AlClH_2^a	15	89	90	-	-
	13	Method in ref. 1 ^b	15	87	90	-	-
	14	AlClH_2^e	5	100	90	-	-

a) The ratio of reducing species to acetal was 1:1.

b) The ratio of $\text{AlCl}_3:\text{LiAlH}_4$:acetal was 1:1:2.c) The ratio of $\text{AlCl}_3:\text{LiAlH}_4$:acetal was 3:1:1.

d) The ratio of reducing species to acetal was 4:1.

e) The ratio of reducing species to acetal was 2:1.

f) Percentages based on total amount of reduction product obtained.

the extent of reduction is 7% in 90 minutes (Table I, expt. 4). Certainly in this case, the action of AlH_3 on the acetal in one minute is negligible. With very reactive acetals, such as 2,2,4-trimethyl-1,3-dioxane the reduction accomplished by AlH_3 in 30 minutes is practically complete (98%) (Table I, expt. 1) while in fifteen minutes it is 64% (Table I, Expt. 2). In one minute the extent of reduction would be in the neighborhood of 5%. We see then, that even in this case the amount of reduction done by the AlH_3 is relatively small. These facts indicate that when the mixture of AlCl_3 and LiAlH_4 is being made, the AlH_3 formed initially does not play an important role in the whole process of reduction.

Furthermore, if we compare the results obtained when the acetal is added to the previously prepared species (Table I, expts. 4, 5, 7, 9, 11, 12), with those obtained following the mixing procedure used by Leggetter and Brown (1) (Table I, expts. 6, 8, 10, 13, 14) we see that they are identical, within the limits of experimental error.

From the work described above and shown in Table I, the following conclusions can be made.

1. a) The addition of the AlCl_3 to the ether solution of acetal or ketal and LiAlH_4 , or, b) prior preparation of the reducing species followed by the addition of the acetal, give the same results.
2. Differences in the ratio of species to acetal are important only if the acetal is a reactive one. For example if we look at experiment 6 in Table I, the ratio of AlClH_2 to acetal is 1:1. In experiment 8, the

ratio of AlClH_2 to acetal is 2:1. However, the extent of reduction of 4-methyl-1,3-dioxolane, a less reactive acetal, is about the same in both experiments.

3. The above observation is not true in the case of reactive acetals. In the case of the 2-phenyl-1,3-dioxane using the species AlClH_2 , the acetal is 100% reduced in 5 minutes (Table I, expt.14). In this experiment the ratio of species to acetal was 2:1. On the other hand, in experiment 12, same Table, where the ratio of the species to acetal was 1:1, the extent of reduction was 89% in 15 minutes. In both experiments, 12 and 14, the reducing procedures were the same; that is, by procedure b, mentioned before.
4. The stronger the Lewis acid character of the reducing species, the greater is its reducing power*. 4-Methyl-1,3-dioxolane is reduced by AlH_3 only 7% in 90 minutes whereas in the same length of time it is reduced to the extent of 90% by AlCl_2H (Table I, expts. 4 and 10).
5. Since in our experiments, and in those performed by Leggetter and Brown, we began with an excess of LiAlH_4 , the first species produced is always AlH_3 ; the next one is AlClH_2 . No AlCl_2H is produced unless more AlCl_3 is added to the reduction mixture. The effective reducing species is therefore AlClH_2 .

* At first sight, this would seem to be in contradiction to the statement that AlClH_2 and AlCl_2H are poorer hydride donors than are AlH_3 or LiAlH_4 . However if carbonium ion formation is a necessary step in the reduction, reducing power is a direct function of Lewis acid character.

6. For those acetals and ketals that produce two products after hydrogenolysis, the proportion of these products is the same regardless of the reducing species used (Table I, last two columns).

II. Methods of Preparing the Acetals and Ketals.

A. Cyclic Acetals and Ketals.

These were prepared following the general procedure in which the aldehyde or ketone was allowed to react with the appropriate diol in the presence of an acid catalyst. The accepted pathway for acetal formation is illustrated in Chart 16, where $n = 0$ or 1.

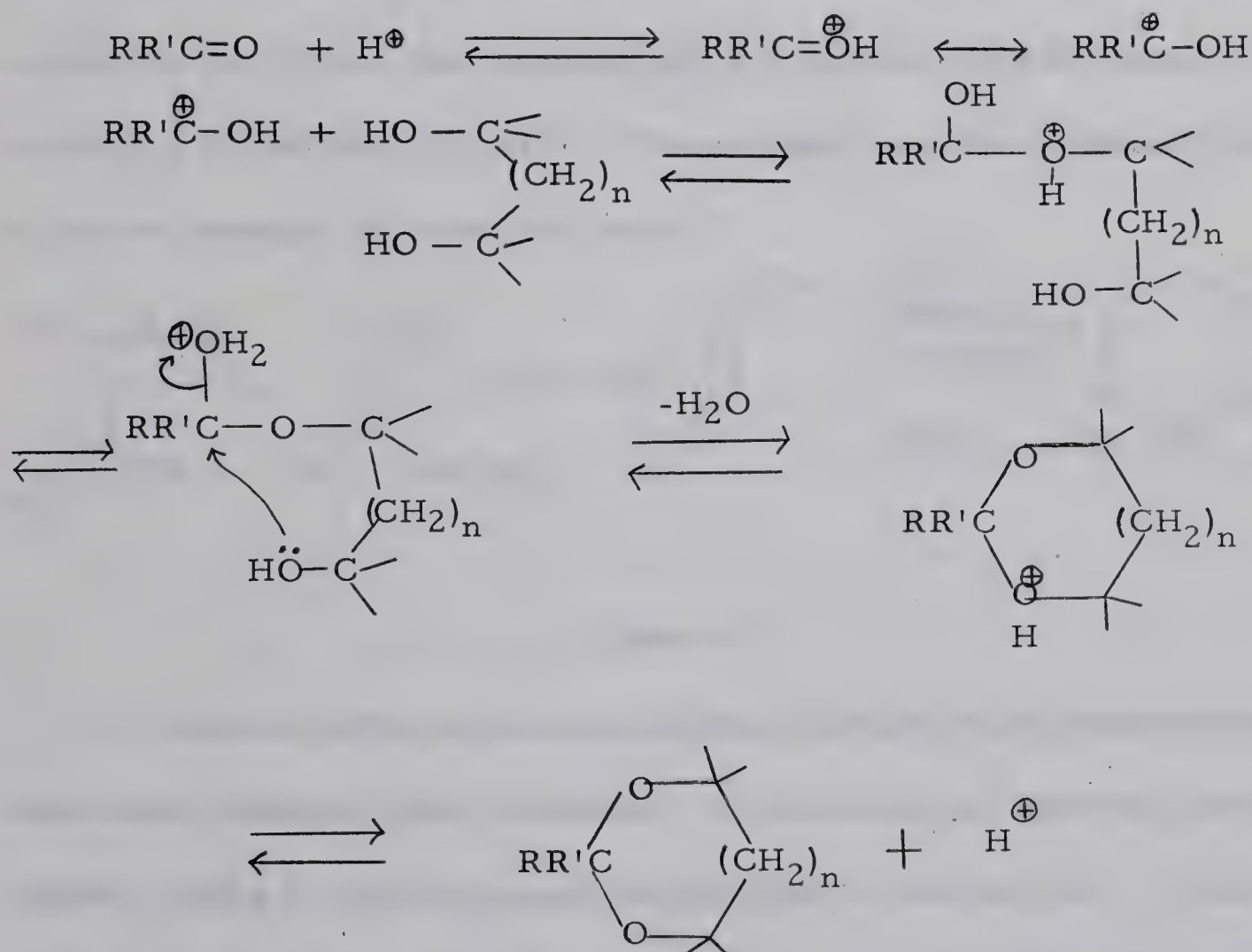


Chart 16

The condensation was carried out either by heating the alcohol (diol) and the carbonyl compound in refluxing benzene or toluene, removing the water by azeotropic distillation, or by dissolving the carbonyl compound and diol in an inert solvent, followed by the addition of a dehydrating agent, and allowing the reaction to proceed at room temperature for a period of time.

B. 2-Alkoxy(aryloxy)tetrahydropyrans

For the preparation of some of the 2-tetrahydropyranyl ethers, a Diels-Alder condensation of an α,β -unsaturated carbonyl compound with a suitable vinyl ether was carried out in a bomb at high temperature according to Longley et al (35). The product was then reduced catalytically. A typical example is shown in Chart 17.

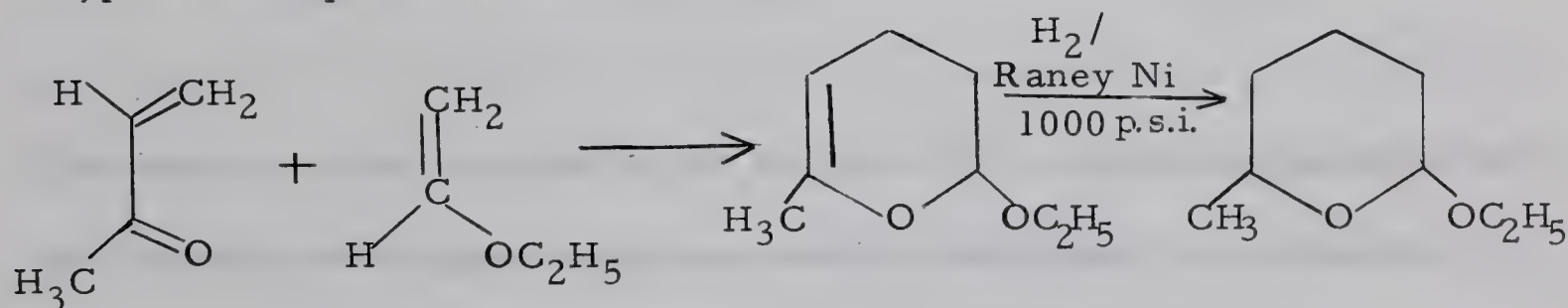
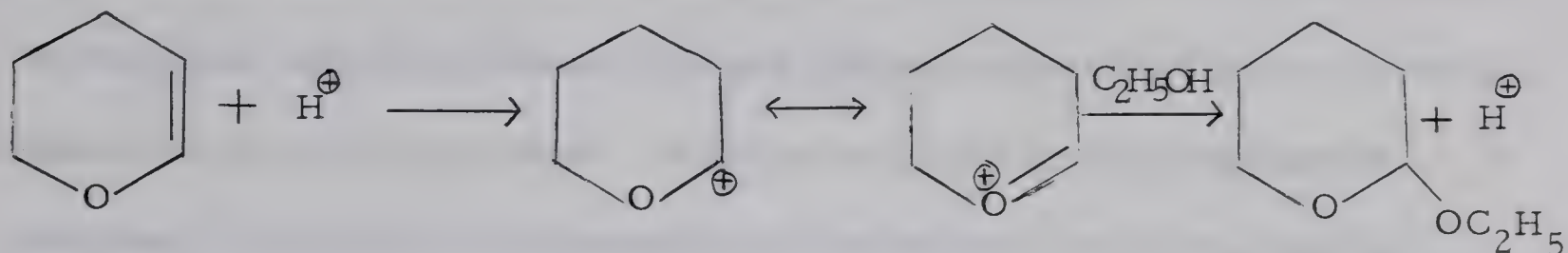


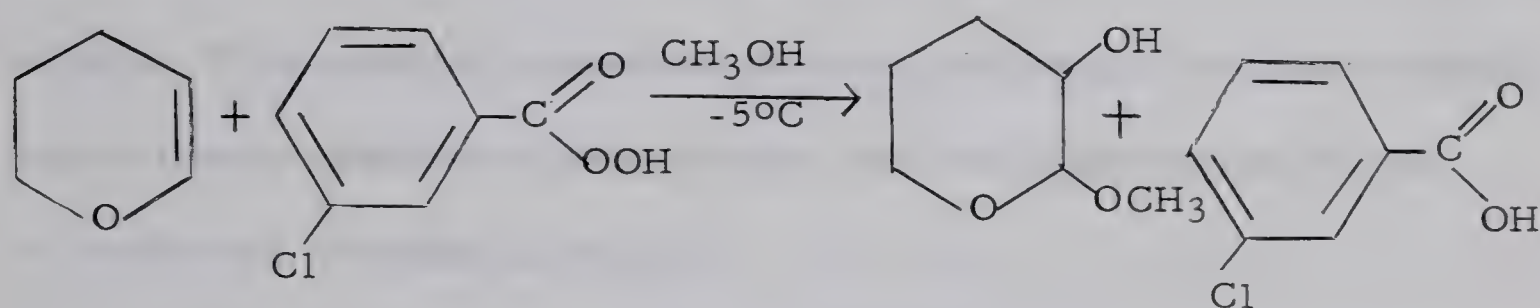
Chart 17

Several of the 2-tetrahydropyranyl ethers were prepared by the reaction of commercially available 4,5-dihydropyran with the corresponding alcohol, using a drop of concentrated HCl as a catalyst (36). This is illustrated in Chart 18 by the formation of 2-ethoxytetrahydropyran. The mechanism postulated requires initial protonation of the 4,5-dihydropyran to yield a carbonium ion, which is stabilized by the participation

of the electron pair of the ring oxygen. A subsequent nucleophilic attack by the alcohol gives the product (37, 38).



For the preparation of the 2-alkoxy derivatives containing a substituent at C_3 , the method given by Sweet and Brown (39) was used. The preparation of 3-hydroxy-2-methoxytetrahydropyran is given as an example.



This method, when applied to the 6-methyl-4,5-dihydropyran provided the 6-methyl homologue which was readily methylated to produce the 3-methoxy derivative. For the preparation of the 2-alkoxy derivatives containing a substituent at C_6 , commercially available 6-hydroxymethyl-4,5-dihydropyran was employed, which was readily converted to the 6-methoxymethyl derivative (40).

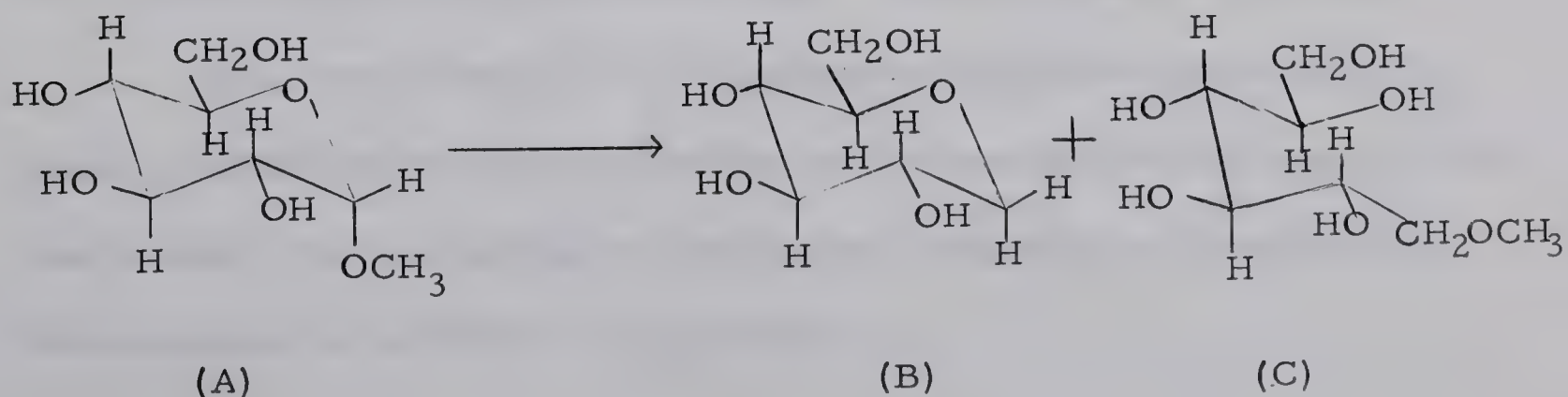
III. General Procedure for Hydrogenolysis.

Most of the reductions were carried out using the procedure followed by Leggetter and Brown (1, 41) which involved the addition of the $AlCl_3$ in ether to an ethereal solution of the $LiAlH_4$ and acetal. The

molar proportions of LiAlH_4 , AlCl_3 and acetal were 1:1:1 and the reduction was done at room temperature. In our case, however, the time of addition of the Lewis acid was reduced to three minutes rather than the ten minutes used by Leggetter and Brown. This proved later to be advantageous because of the more rapid formation of the effective reducing species. In some of the later experiments, the reduction procedure differed from that followed in the earlier experiments. In these cases the AlCl_3 in ether was added to the LiAlH_4 also in ether, thus forming the particular reducing species (32). After approximately five minutes the acetal was added. This modified procedure gave results identical to those obtained by the first procedure which is the one used by Leggetter and Brown in their work on cyclic acetals (1).

IV. A Possible Correlation Between Hydrolysis and Hydrogenolysis.

Since alkyl glycosides are acetals, it was anticipated that hydrogenolysis by the mixed reagent would be feasible. Two products should be formed. For example, reduction of methyl α -D-glucopyranoside (A), theoretically would produce the structures (B) and/or (C).



From the work described in the introduction, it can be expected that the nature of the substituents, their position in the ring, the size of the ring and also the nature of the aglycon group should affect the rate and direction of cleavage of these glycosides. The work of Kreevoy and Taft (19, 20) clearly showed that electronic effects are of importance in determining the rate of hydrolysis of acetals and ketals. The work by Leutner (21-24), Ceder (25) and Salomaa (26) also demonstrated this fact. Leggetter and Brown (1) pointed out that those substituents which increase the rate of hydrogenolysis of cyclic acetals also increase the rate of hydrolysis of acyclic and cyclic acetals. In all cases electron donor substituents attached to the anomeric carbon increase the speed of both hydrolysis and hydrogenolysis. The same mechanistic interpretation is offered for both processes, involving the formation of an intermediate carbonium ion as the rate determining step.

Much work has been done concerning the problem of the mechanism of acid-catalyzed hydrolysis of glycosides. Two mechanisms have been proposed. One of them, termed the A-1 (B) mechanism, involves opening of the ring. The other mechanism, designated by the term A-1 (A), proceeds via ring retention (42). This is shown in Chart 18.

Since what actually occurs during the reduction of acetals is the trapping of the intermediate carbonium ion by reaction with the hydride, it was thought that the hydrogenolysis reaction might throw some light on the mechanism of hydrolysis of glycosides.

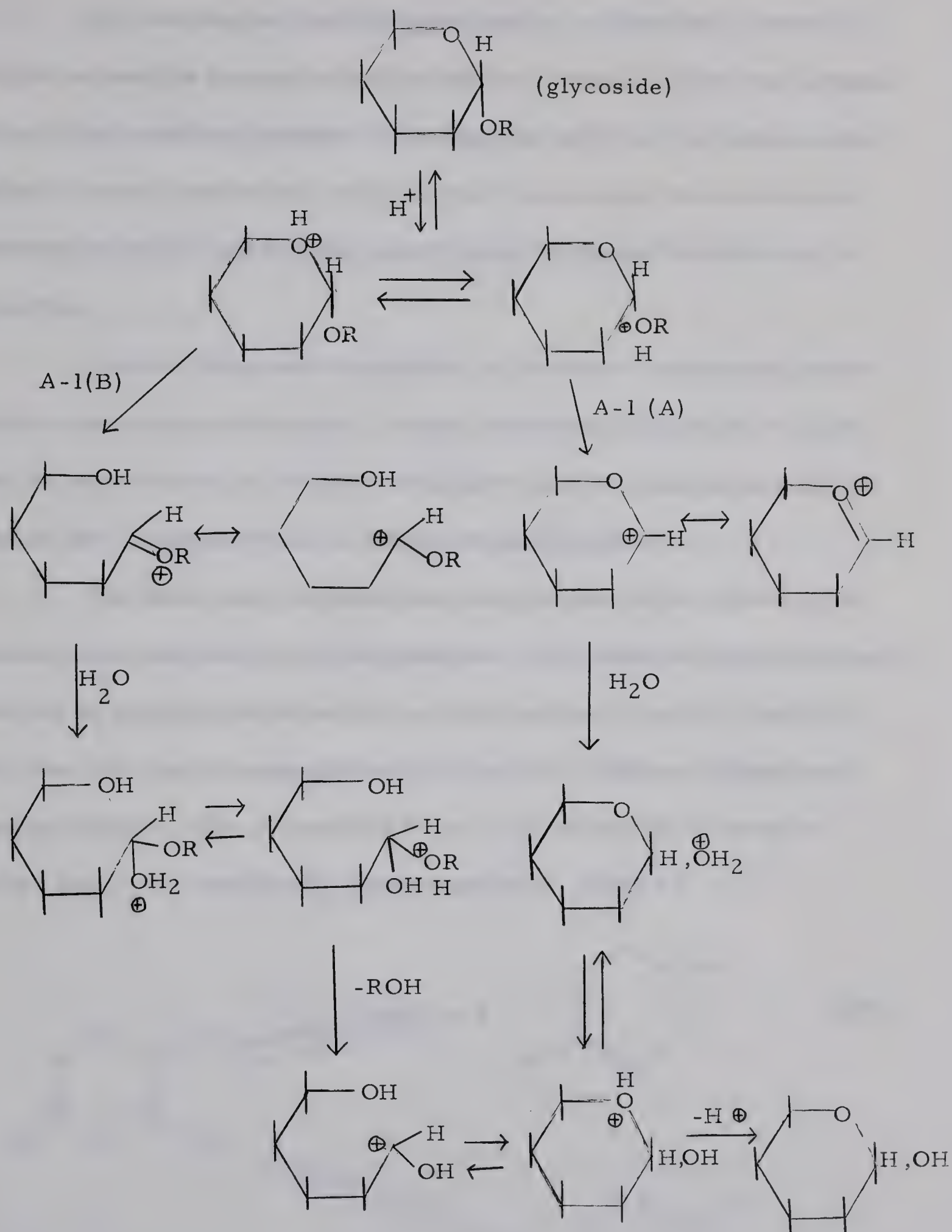
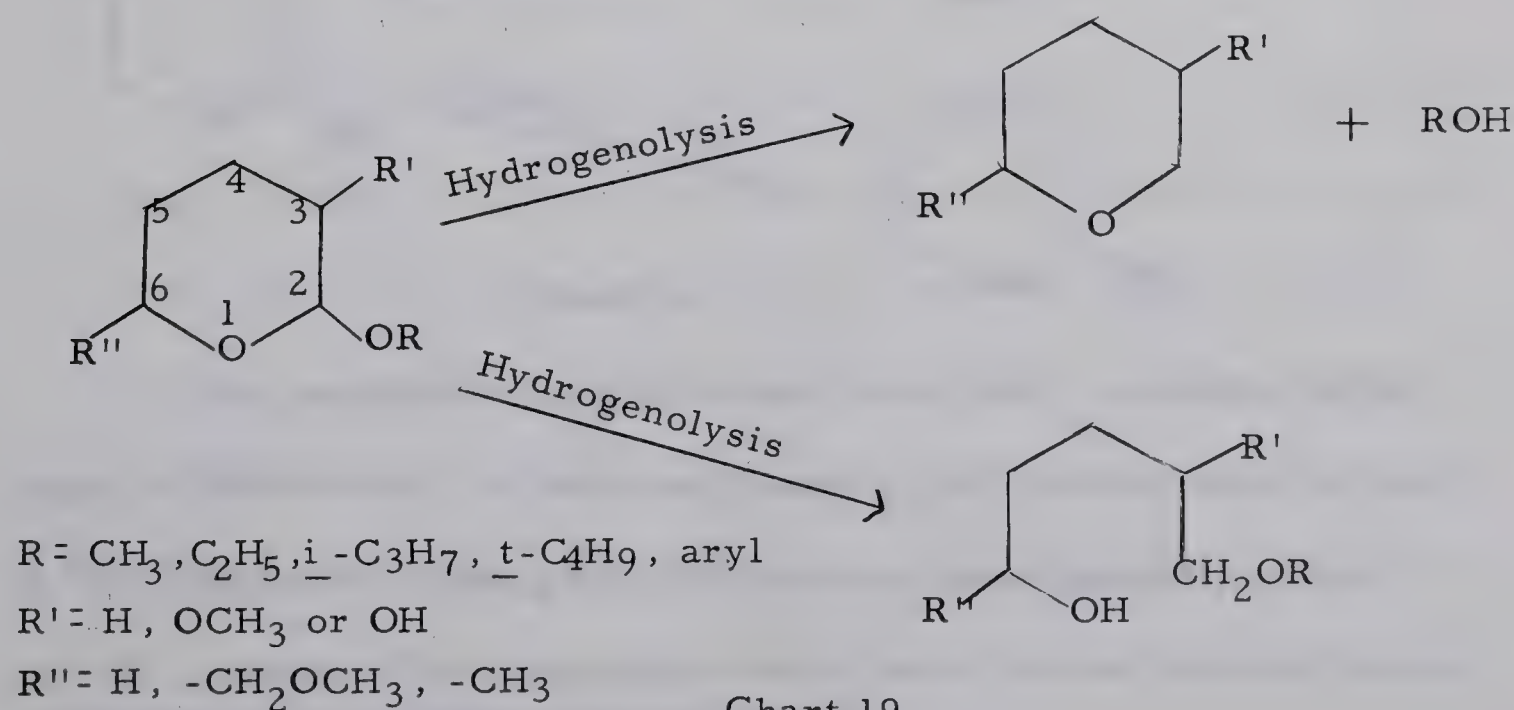


Chart 18

By carrying out the hydrogenolysis of a glycoside in ether it might be possible to trap the carbonium ion formed. From the composition of the reduction products containing the cyclic or the acyclic ether or both, some conclusions could be drawn concerning the mechanistic pathway followed, and how the substituents influenced the direction of reaction.

Before trying such reductions on the more complicated carbohydrate structures themselves, it was considered instructive to carry out the experiments on simpler compounds such as 2-alkoxytetrahydropyrans and ring substituted 2-alkoxytetrahydropyrans.

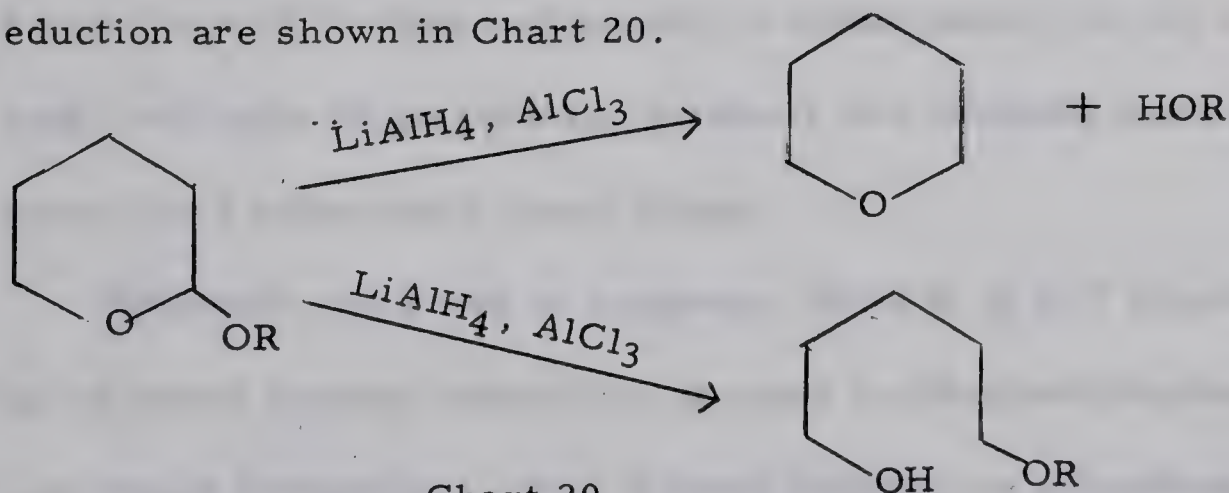
The work which follows describes studies of the influence on the direction and extent of hydrogenolysis, of 2-alkoxytetrahydropyrans, exerted by substituents R' and R'' at ring positions 3 and 6, Chart 19. Included also was an examination of the effect of different alkoxy and aryloxy groups, $-OR$, at position 2, on the preferential cleavage of either the C_2-O_1 bond or C_2 -exo oxygen bond, Chart 19.



Some trial experiments were carried out on the hydrogenolysis of methyl 2,3,4,6-tetra-O-methyl- α -D-glucopyranoside and methyl 2-deoxy-3,4,6-tri-O-methyl- α -D-glucopyranoside, the results of which can be seen later on in this section.

V. Hydrogenolysis by the Mixed Reagent of 2-Alkoxy- and 2-Aryloxy-tetrahydropyrans.*

A series of 2-alkoxytetrahydropyrans and 2-aryloxytetrahydropyrans were subjected at room temperature to hydrogenolysis, using equimolar quantities of AlCl_3 , LiAlH_4 and the tetrahydropyranyl ether. The alkyl substituents, R, were chosen to provide a spectrum of primary, secondary and tertiary groups, while the aryl groups, R, were suitably chosen phenyl rings, substituted by electron donating or electron attracting groups. The conditions for the reductions and work-up were in all cases the same, as much as experimentally possible. The two pathways for the reduction are shown in Chart 20.



The recovery of materials was very good, generally in the range of 78% to 95%. In only one case was the total recovery as low as 72%. Since the hydrogenolysis products are obtained by a non-

*All the reductions throughout this thesis were carried out with the d-1 mixtures of the tetrahydropyranyl ethers.

reversible process, and are stable under the reaction conditions, and because of the good recovery of materials, the yield of products could be used as a reasonable measure of the preferential route of reaction (Chart 20).

The results of these experiments are shown in Table II (a). Some important general observations can be made from an examination of the data shown in Table II a.

1. The proportion of ring cleavage to side chain cleavage (Chart 20) increases as the alkyl group R is changed from primary to tertiary (Table II a, expts. 1-4 and 10, 11) ranging from 30% ring cleavage when $R = \text{CH}_3$ to 87% ring cleavage when $R = \text{t-butyl}$.
2. Only in the case where the alkyl group R is $-\text{CH}_3$ is the proportion of ring cleavage to side chain cleavage less than unity (70% side chain cleavage).
3. Regardless of the type and number of substituents on the aromatic ring, only side chain cleavage products are obtained when R is a phenyl or a substituted phenyl group.

While this work was in progress, Eliel et al (27) reported their results of mixed hydride reductions of some 2-alkoxytetrahydropyrans. For convenient comparison some of their results are reproduced in Table II(b). They, also, found that the proportion of ring cleavage to side chain cleavage increased as R changed from a primary alkyl group to a tertiary alkyl group. The amount of ring cleavage obtained by them

TABLE II(a)

Hydrogenolysis of Some 2-Alkoxy- and 2-Aryloxytetrahydropyrans.

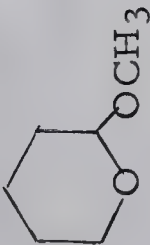
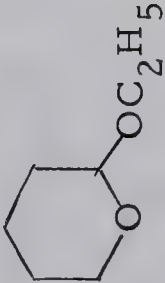
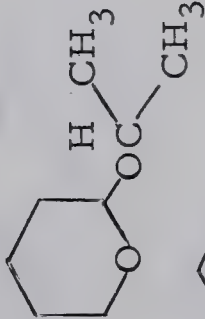
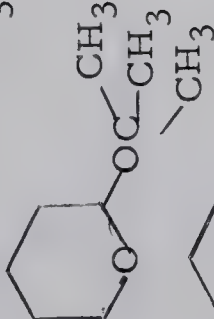
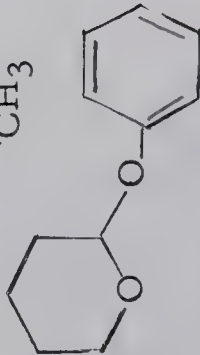
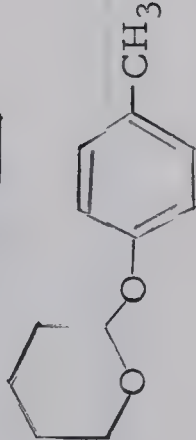
Compound	Expt. No.	Reduction Time, hr.	Extent of Reduction, %	Side Chain Cleavage, %	Ring Cleavage, %	Recovery of Materials, %
	1	16	100	70	30	82
	2	12	100	40	60	85
	3	3.5	100	18	82	79
	4	21	100	13	87	88
	5	24	100	100	0	72
	6	24	100	100	0	97

TABLE II(a) - Continued

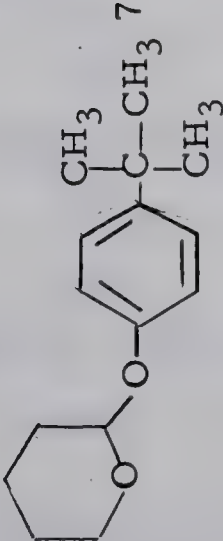
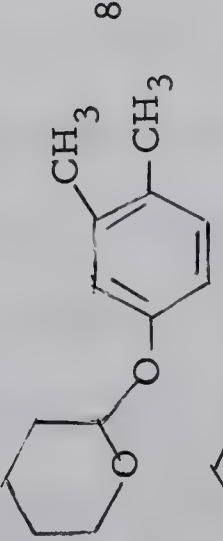
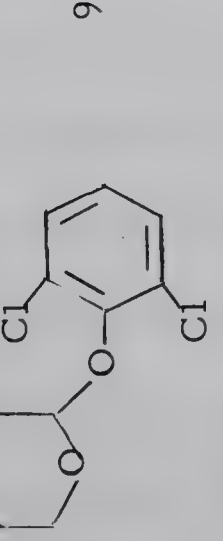
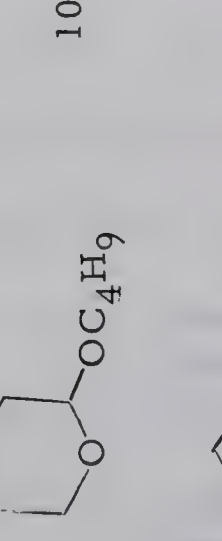
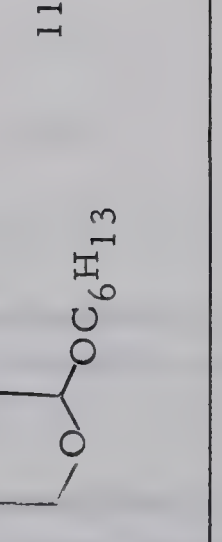
Compound	Expt. No.	Reduction Time, hr.	Extent of Reduction, %	Side Chain Cleavage, %	Ring Cleavage, %	Recovery of Materials, %
	7	24	100	100	0	78
	8	24	100	100	0	84
	9	24	100	100	0	80
	10	17	100	40	60	88
	11	17	100	55	45	83

TABLE II (b)

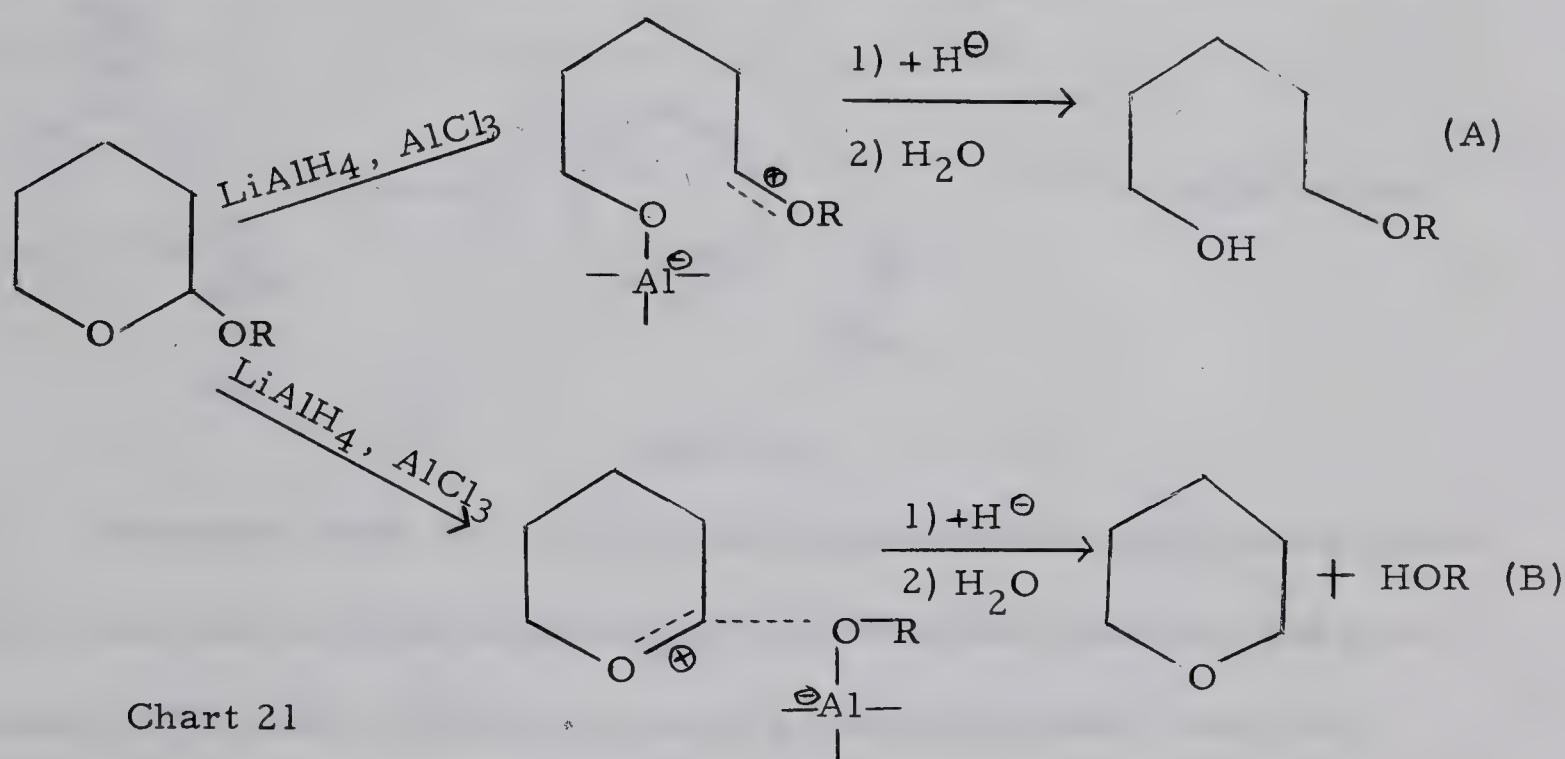
Hydrogenolysis of Some Tetrahydropyranyl Ethers.*

Compound	Expt. No.**	Side Chain Cleavage % Yield	Ring Opening % Yield
	12	not determined	72
	13	not determined	79
	14	not determined	43
	15	13	51
	16	38	45
	17	38	10
	18	90	11
	19	15	27
	20	47	non isolated, yield small or nil
	21	94	non isolated, yield small or nil

*Taken from Eliel's work (27).

**All reduction times are 2 hours.

was as low as 10% for some primary alkyl groups. It is noteworthy that the ratio of ring cleavage to side chain cleavage found by Eliel *et al* for the primary R groups differed considerably from those found in our work. On the basis of their results they suggested that polar factors were no doubt involved in determining the direction of cleavage, as had been pointed out by Leggetter and Brown for the substituted 1,3-dioxolanes and 1,3-dioxanes (1). In the two routes of cleavage (Chart 21), the oxo-



carbonium ion obtained by ring opening (route A) would be stabilized to a greater extent when R is a tertiary alkyl group. Hence, this would be the preferred course of reaction (Table II(b), expt. 4). However, since they found that the neopentyl group (primary) afforded 27% of ring opening (Table II(b), expt. 12) while the *n*-butyl or the *n*-hexyl group (both primary) gave only 10% and 11% ring opening respectively (Table II(b), expts. 17 and 18), another factor was suggested as being operative. This they believed was of steric origin. A bulky R group should hinder attachment of the

Lewis acid to the exo oxygen adjacent to R (Chart 22, route B), and hence, preferential coordination of the Lewis acid with the ring oxygen would result in a greater proportion of ring cleavage.

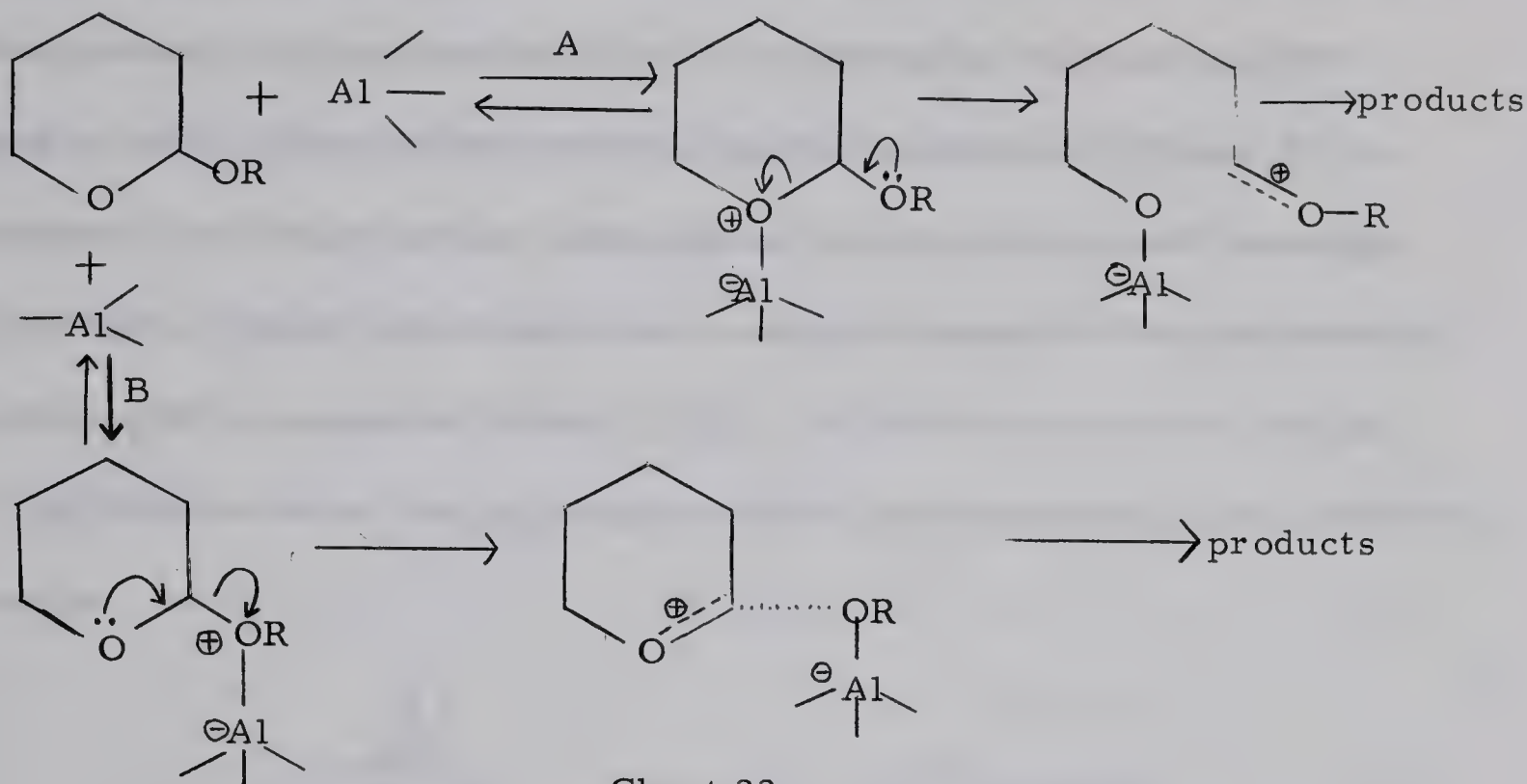


Chart 22

However, when $R = -C(CF_3)(CH_3)_2$ (an electron withdrawing group which is also as bulky as the t-butyl group) side chain cleavage was predominant (47% yield) with little or no ring cleavage product observed (Table II(b), expt. 20). This preference was attributed to polar effects overriding the steric hindrance to attack by the Lewis acid on the exo-oxygen. A similar overriding polar effect was invoked to account for the observation that when $R = C_6H_5CH_2CH_2-$, 94% of the product was the result of side chain cleavage with no isolable ring cleavage product (Table II(b), expt. 21). The nearly exclusive side chain cleavage of both 6-methyl-2-isopropoxytetrahydropyran and 6-hydroxymethyl-2-methoxytetrahydropyran was attributed to the steric interference of the 6-methyl and 6-hydroxy-

methyl groups to association of the Lewis acid with the ring oxygen.

On the basis of the results obtained a further suggestion was made by these workers that the 2-alkoxytetrahydropyrans, when R is an n-alkyl group, would exist preferentially in the conformation wherein the -OR group is axial, in accordance with the anomeric effect (43) (Chart 23, a). But when R is a bulky tertiary alkyl group, steric effects could outweigh the anomeric (polar) effect and thus cause preference for the conformation in which -OR is equatorial (Chart 23, b). In (a) the structure is set up for "anti" elimination of the exo oxygen moiety, and hence this is the preferred reaction.

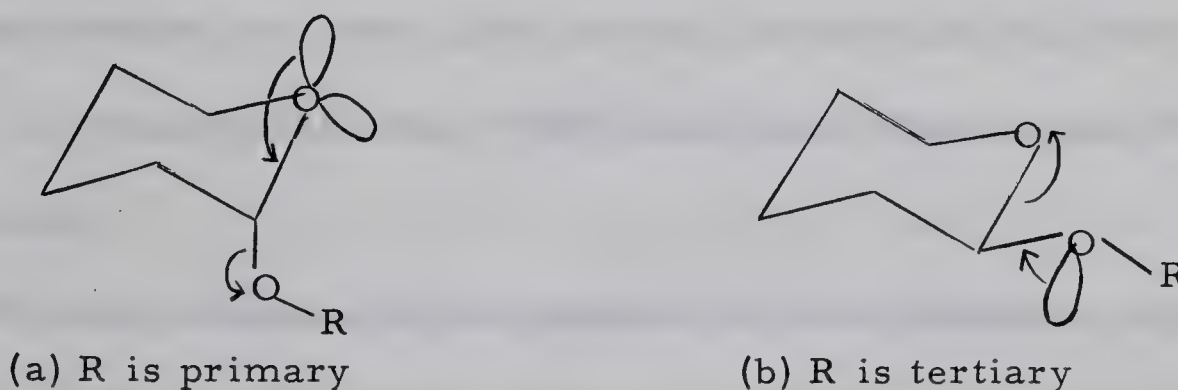


Chart 23

In (b) the structure favors "anti" elimination of the ring oxygen, thus accounting for the preponderance of ring opening.

Quantitative or near quantitative recovery of reactants and products is essential as a basis for such arguments. Examination of the work reported by these authors (27) (Table II(b), expts. 12-21) reveals that several of the experiments gave a low recovery. Experiments 14, 17 and 19 gave 43%, 48% and 42% respectively. Furthermore a repetition in our laboratory of the hydrogenolysis of 2-n-butoxy- and 2-n-hexoxytetra-

hydropyran, using both their method and our method gave a recovery of 88% and 83.5% respectively. But of greater significance is the fact that our work revealed that the amount of ring cleavage was 60% and 45% rather than 10% and 11% respectively. In view of the poor recovery (yield) found for some of their experiments several of which are quite crucial to the mechanistic proposals above, and because of the discrepancies just mentioned between our hydrogenolysis results and theirs, there is some doubt concerning the soundness of their conclusions.

It is our view that polar effects are the predominant factors which determine the direction of reductive cleavage. A steric factor such as the bulky effect between the Lewis acid and the R substituent may have some bearing, but is of significance only when polar factors cancel out, or in certain special cases.

Of some relevance to this question of steric influence is the observation by Leggetter and Brown (18, 44) that the hydrogenolysis of 2,2,4-trimethyl-1,3-dioxolane using LiAlH_4 with either BF_3 or AlCl_3 gave the same results (Chart 24).

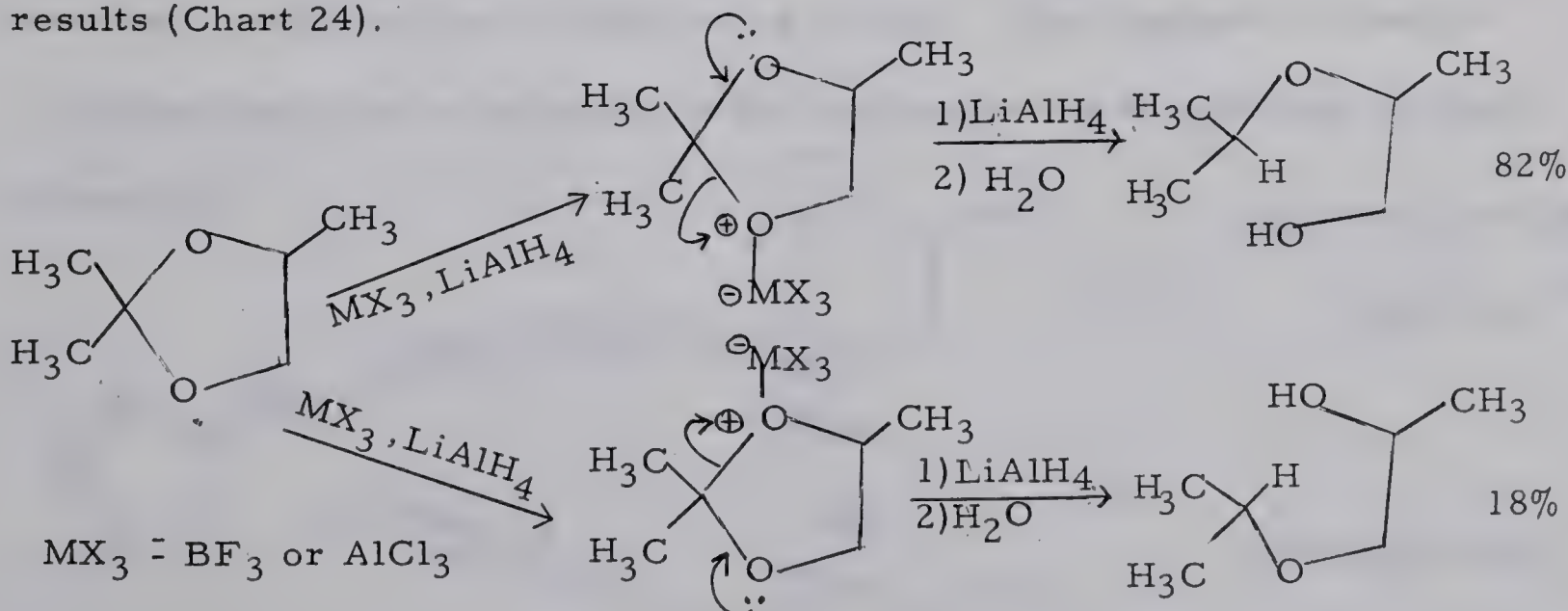
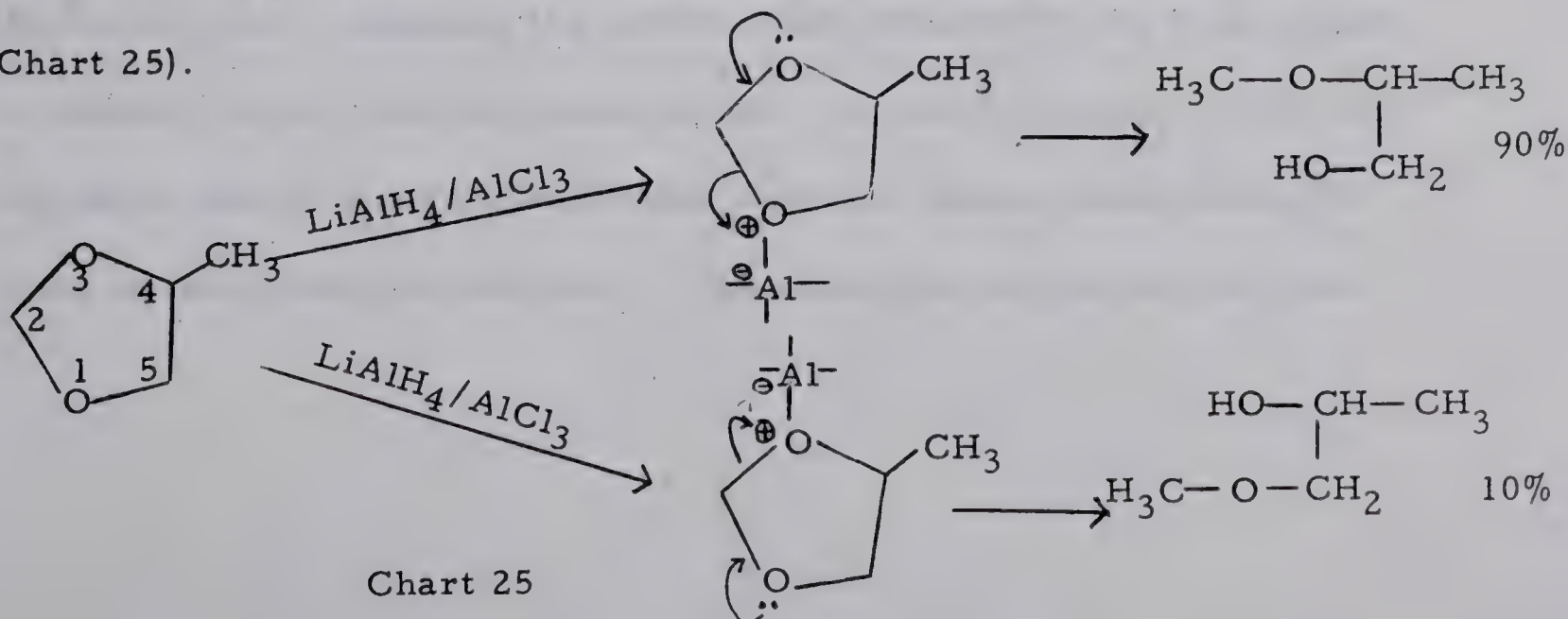


Chart 24

This was interpreted as indicating that steric interference to approach of the Lewis acid plays no significant role in this case. The diameter of a boron atom is ~ 0.6 of the diameter of the aluminum atom. The diameter of a fluorine atom is ~ 0.5 of the diameter of the chlorine atom. However, in spite of the smaller size of the Lewis acid BF_3 , the direction of ring opening was the same as that found where AlCl_3 was used. However, we don't know what the state of aggregation or complexing of the Lewis acid is in ether solution, and the total complex in both the aluminum and the boron species might be large enough, so that there is no difference in steric effects, i.e., the steric factor might therefore be the same for both cases.

A comparison of the results obtained by Leggetter and Brown (1) with those obtained in this work on the hydrogenolysis of the substituted tetrahydropyrans leads to some interesting and pertinent conclusions. They found that electron donor substituents at C_4 in the 1,3-dioxolanes will favor cleavage of the C_2 -O bond farther from the substituted carbon. The reverse is true for electron attracting groups. For example, 4-methyl-1,3-dioxolane gave on reduction 90% of the product as the primary alcohol, (Chart 25).



To facilitate the comparison between the results obtained with the 1,3-dioxolanes (1) and those from the tetrahydropyranyl ethers in the present work, the structure of 4-methyl-1,3-dioxolane is depicted as shown below (Chart 26, a). If one imagines a division of the molecule as shown by the dotted line, it is seen that oxygen #1 has a methylene neighbor attached to it, which can be considered as playing the role of a methyl group. Oxygen #3 has the equivalent of an ethyl group ($-\underset{\text{H}}{\text{C}}_4-\text{CH}_3$) attached to it. In comparison, the ring oxygen of 2-methoxytetrahydropyran (Chart 26, b) has the equivalent of an ethyl group attached to it

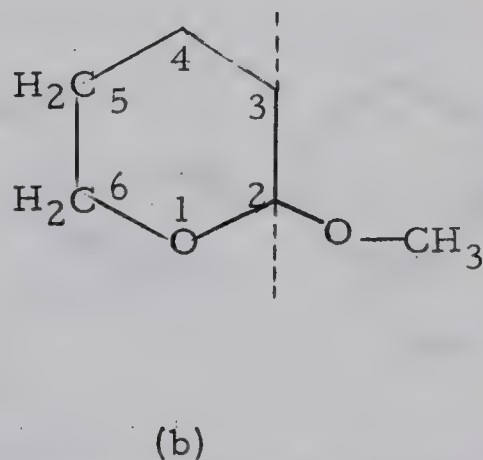
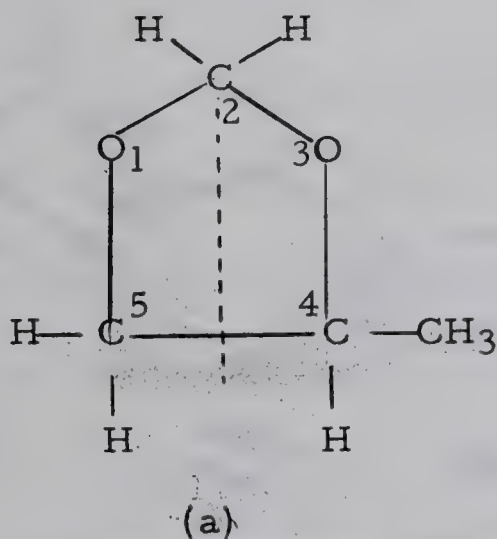
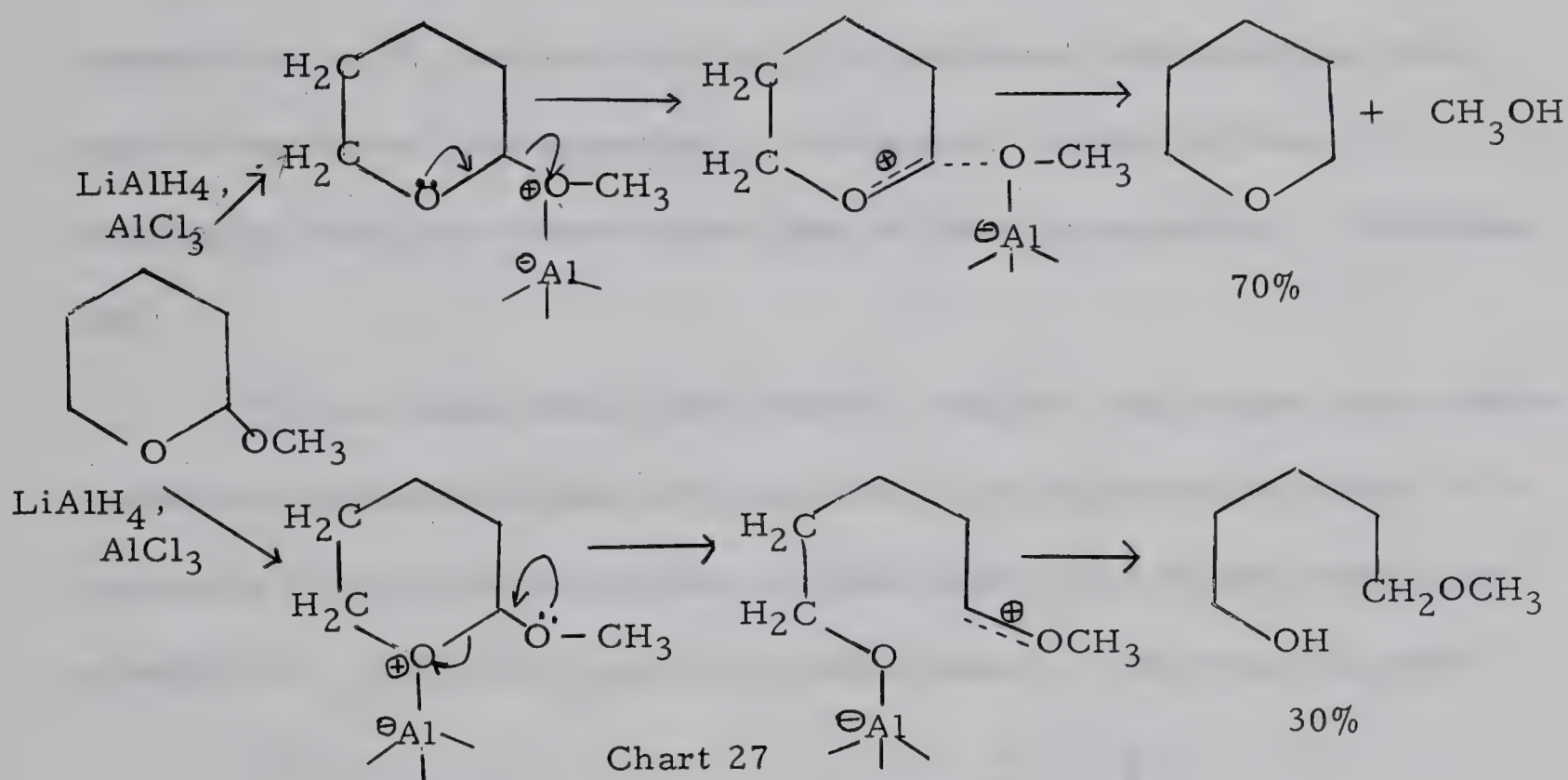


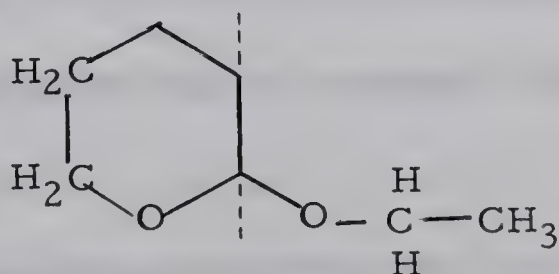
Chart 26

($\text{H}_2\overset{5}{\text{C}}-\overset{6}{\text{CH}_2}\text{O}-$). Although the carbon chain attached to the ring oxygen is actually larger than two carbon atoms, we don't consider significant any polar effects transmitted farther than two carbon atoms along the chain of saturated hydrocarbons. The exocyclic oxygen has only one

carbon attached to it, that of the methyl group. If polar effects are pre-dominant, we can expect more side chain cleavage since an ethyl group is a better electron donor than is a methyl group. This also follows the view held by Leggetter and Brown (1) that stabilization of the intermediate oxocarbenium ion by the ethyl group is greater than by the methyl group. And this is precisely the result in our work. The extent of side chain cleavage is 70% and of ring cleavage is 30% (Chart 27).



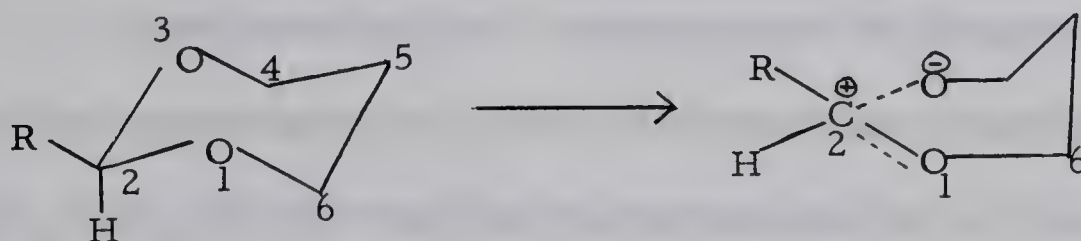
Considering the 2-ethoxytetrahydropyran in the same manner we see by inspection of the structure that both the ring oxygen and the exo oxygen have an ethyl group or its equivalent attached.



We would expect little or no preferential cleavage since the oxo-carbonium ion obtained by ring cleavage or by side chain cleavage should be equally stabilized. The experimental results show 40% side chain cleavage and 60% ring cleavage. It is possible here that since the polar effects are equal the effect of six-membered ring conformation comes into play.

It has been shown by Leggetter, Diner and Brown (41) that C_2 -unsubstituted or C_2 -monosubstituted 1,3-dioxolanes hydrogenolyze more rapidly than do the corresponding 1,3-dioxanes. Similarly these 1,3-dioxolanes hydrolyze 6 times faster than do the corresponding 1,3-dioxanes (24).

The rationale behind these facts is that for ring oxygen participation to stabilize the intermediate carbonium ion in the 6-membered rings, it is necessary for the ring to approach the half chair conformation (see below) in which R, C_2 , O_1 and C_6 are in the same plane. This requires some



degree of distortion with consequent decrease in reactivity. This degree of distortion is much less in the case of 1,3-dioxolanes, since they are five-membered rings and more nearly coplanar initially than are the 1,3-dioxanes.

For the 2-ethoxytetrahydropyran this kind of distortion with

consequent retarded reaction can be avoided if the exocyclic oxygen (Chart 28, a) rather than the ring oxygen (Chart 28, b) participates in carbonium ion stabilization.

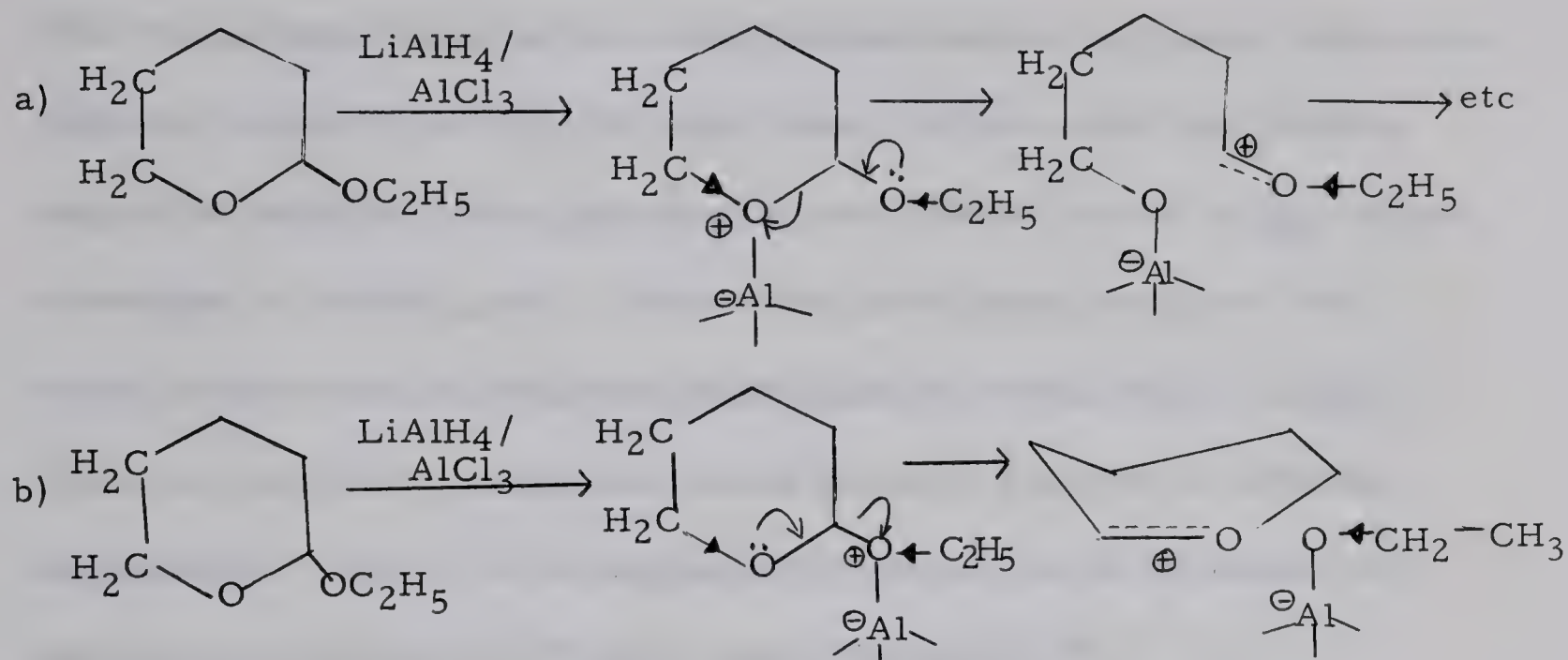


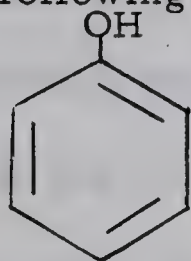
Chart 28

The overall effect then, is that ring cleavage is slightly favored.

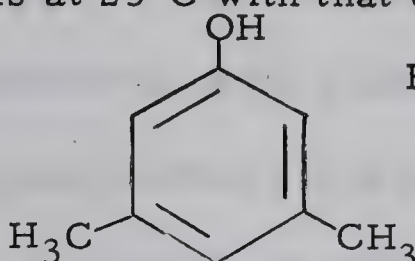
In the case of 2-methoxytetrahydropyran the electronic effects outweigh this, and side chain cleavage predominates.

If we examine the 2-isopropoxytetrahydropyran we observe that the ring oxygen again is joined to the equivalent to an ethyl group ($\text{H}_2\text{C}_5\text{-H}_2\text{C}_6\text{-O}$) whereas the exo oxygen has now an isopropyl group attached to it. We might expect now that ring cleavage should be the preferred route. The experimental result shows that this mode of cleavage actually does occur to the extent of 82%. Finally the 2-t-butoxytetrahydropyran gives on hydrogenolysis 87% ring cleavage as expected from the foregoing analysis.

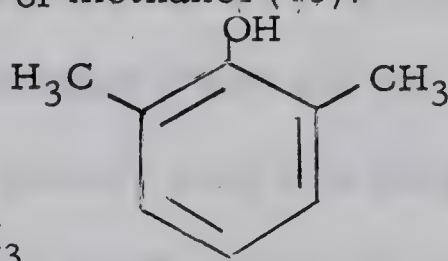
If we look at the results of the hydrogenolysis of the aryloxy derivatives (Table II, expts. 5-9) in all cases the predominant, if not exclusive pathway of reduction is side chain cleavage. This is so even when the aromatic ring has two methyl substituents or a *t*-butyl substituent. Applying the above rationale to these cases, we see again that the ring oxygen has attached to it a group equivalent to ethyl, while the exo oxygen is attached to an aryl group. Even if the aryl group possesses two methyl substituents the electron donating ability of the ring to the exo oxygen is considerably less than that of the ethyl group to its attached oxygen atom. This view is supported by comparison of the acidity of the following phenols at 25°C with that of methanol (45).



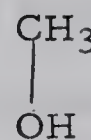
$pK_a = 9.99$



10.18



10.58



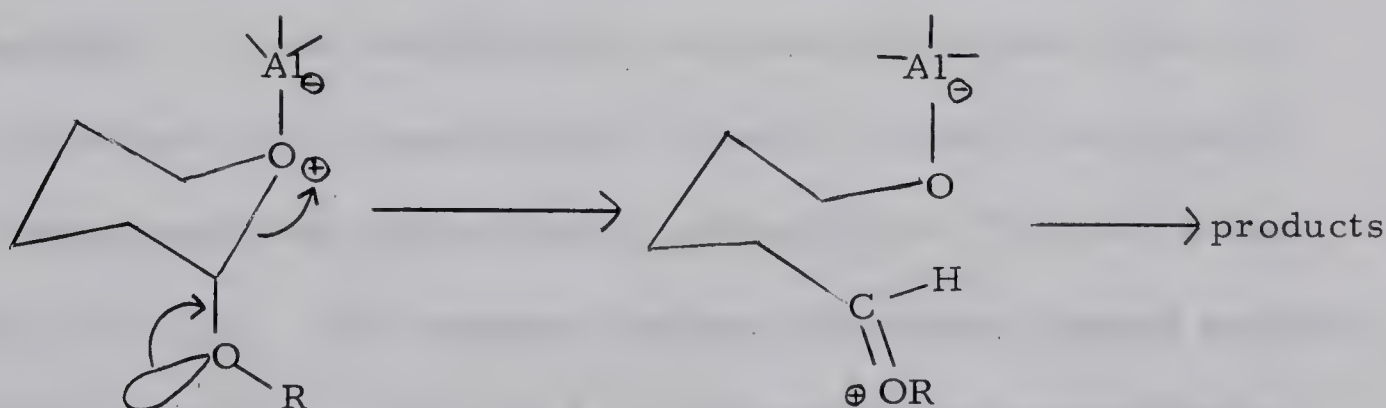
18

One might expect, in the case of 2-(2,6-dichlorophenoxy)tetrahydropyran that the two chlorine substituents in the ortho positions would hinder Lewis acid association with the exo oxygen and accordingly, by alternative association of the Lewis acid with the ring oxygen, give rise to some ring cleavage product on hydrogenolysis. However the experimental result is 100% side chain cleavage.

The sum total of the above results indicates that steric effects if present, are outweighed by polar or electronic effects in their influence

on the direction of bond cleavage.

We believe that a very minor role (if any) is played by the proposal that primary alkyl groups R will permit a greater abundance of the conformer which has the -OR group in the axial position, thus, favoring anti elimination of the exo oxygen unit (27). This concept was based on the 10% to 11% ring cleavage found for the n-butoxy and n-hexoxy compounds. Since in our work the ethoxy group (R also primary) produces 60% ring cleavage and the above figures (10 and 11%) were not substantiated by our work, the main support for the above postulate has been removed. If anti elimination is still a necessary requisite, and if the Lewis acid associates with the ring oxygen, and assuming the predominance of the conformer which has the -OR group axial due to the anomeric effect, it is clearly seen that the exo oxygen can rotate about the C-O bond and orient itself so that the lone electron pair become trans to the C₁-ring-oxygen bond. In this way anti elimination can still take place as shown below, but now resulting in

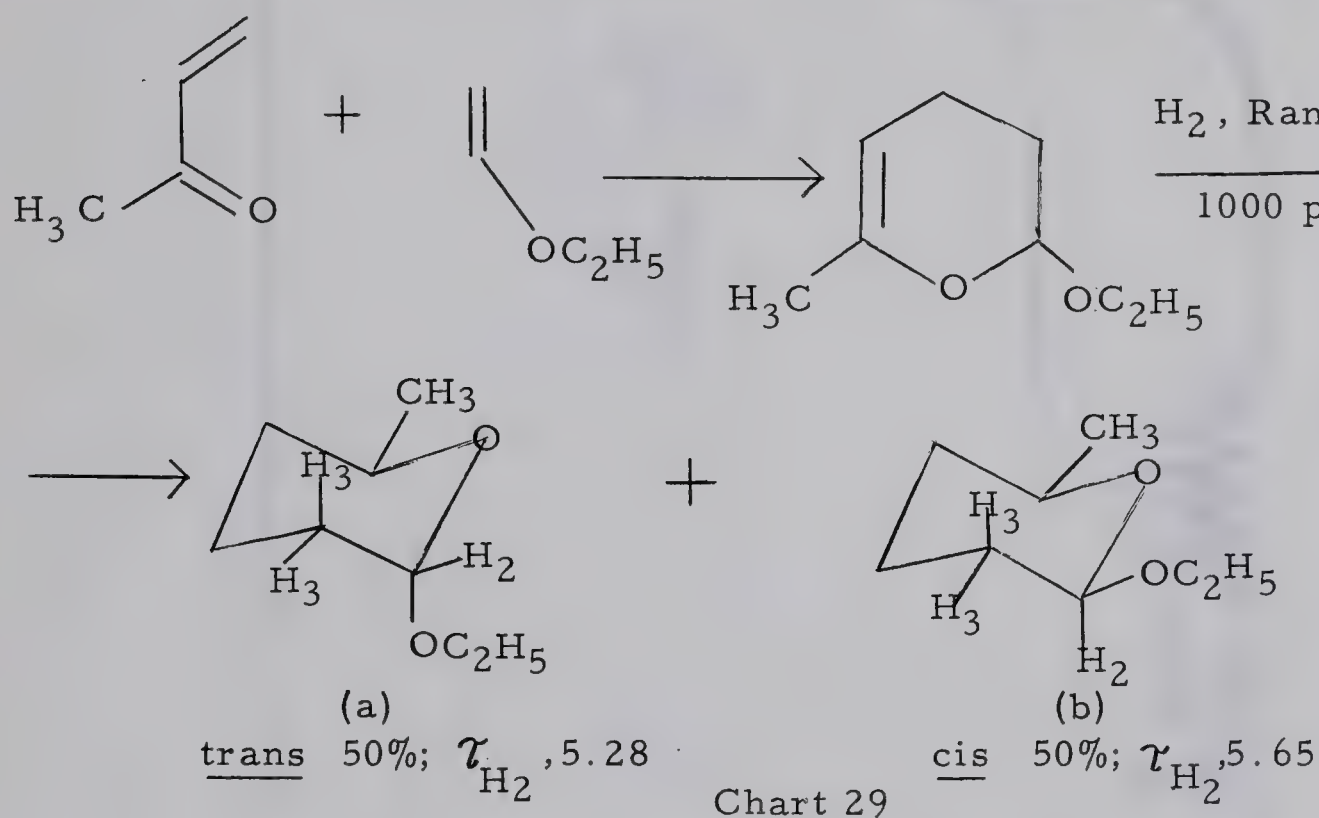


ring cleavage.

Hence, it is not necessary to have -OR equatorial for favored anti elimination of the ring-oxygen unit.

VI. Hydrogenolysis by the Mixed Reagent of 6-Substituted-2-alkoxy-tetrahydropyrans.

The synthesis of 2-ethoxy-6-methyltetrahydropyran (Chart 29) gave a mixture of cis and trans isomers. Gas liquid chromatography showed two distinct peaks in a 1:1 ratio. This was confirmed by the n.m.r. spectrum of the cis-trans mixture (Fig. 1).



The individual isomers were separated quite readily by gas liquid chromatography. Their configuration was readily assigned (Chart 29, a and b), from the n.m.r. spectra (Figs. 2 and 3). One of the isomers showed a broad singlet for the anomeric proton (H_2) at τ , 5.28, with a half-width of 4 c.p.s.. The anomeric proton of the other isomer exhibited a doublet at τ , 5.65 ($J_{2,3} = 9$ c.p.s.). It is known from carbohydrate chemistry and from the study of cyclohexane systems (43, 46, 47) that the axial protons resonate at higher field than do equatorial protons. In

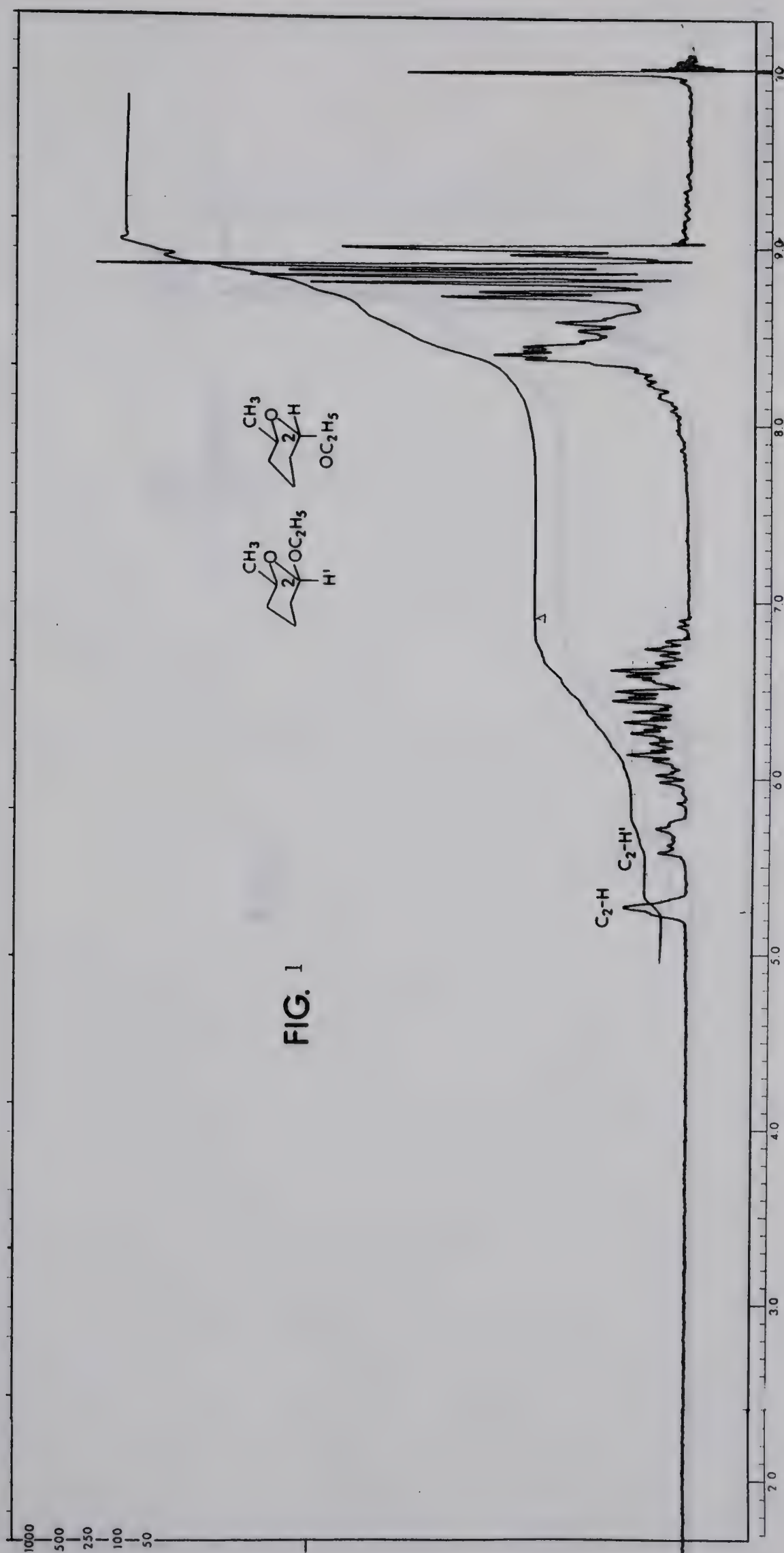


FIG. 1

N.m.r. spectrum of the cis, trans mixture of 2-ethoxy-6-methyltetrahydropyran.

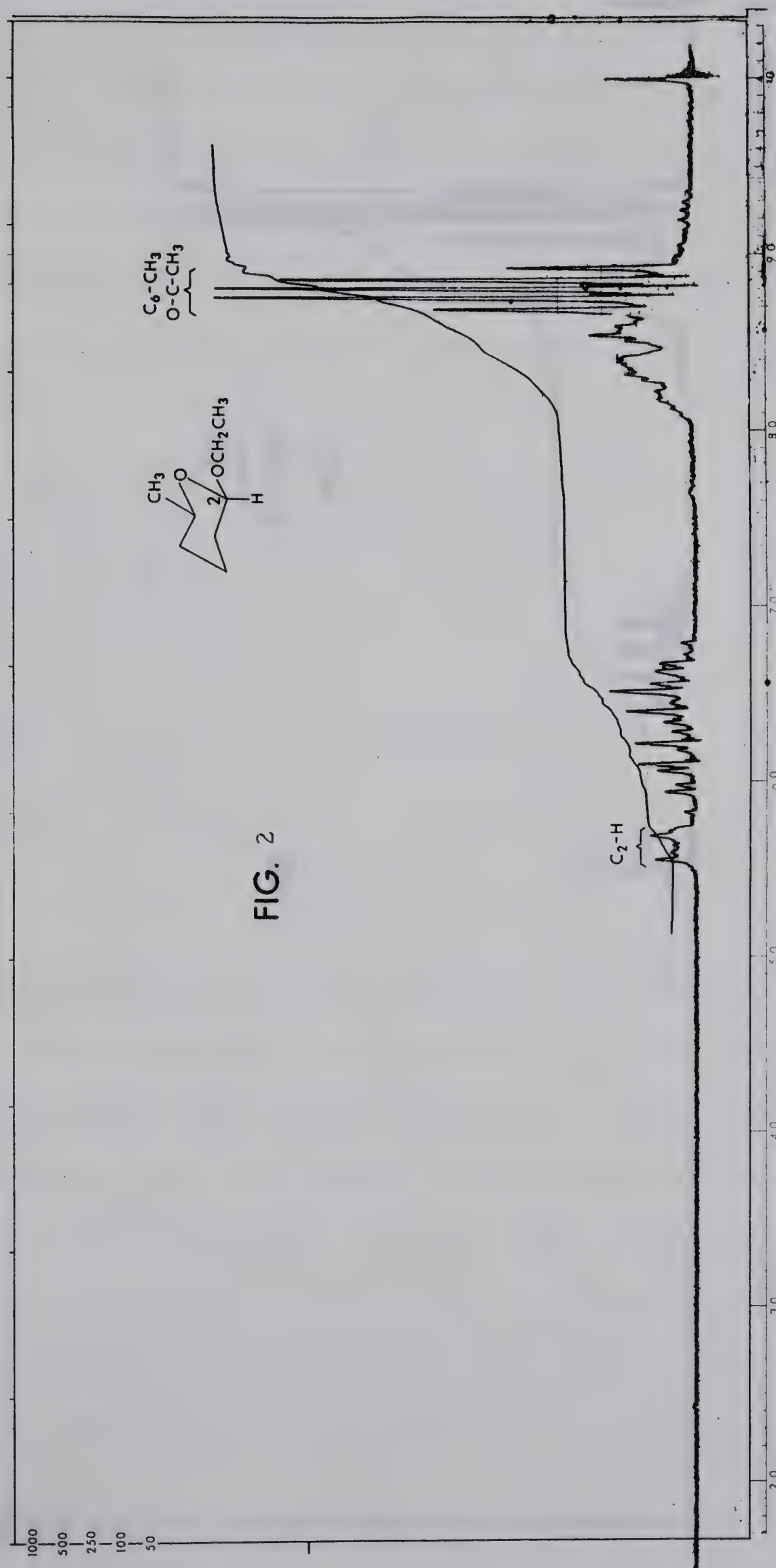
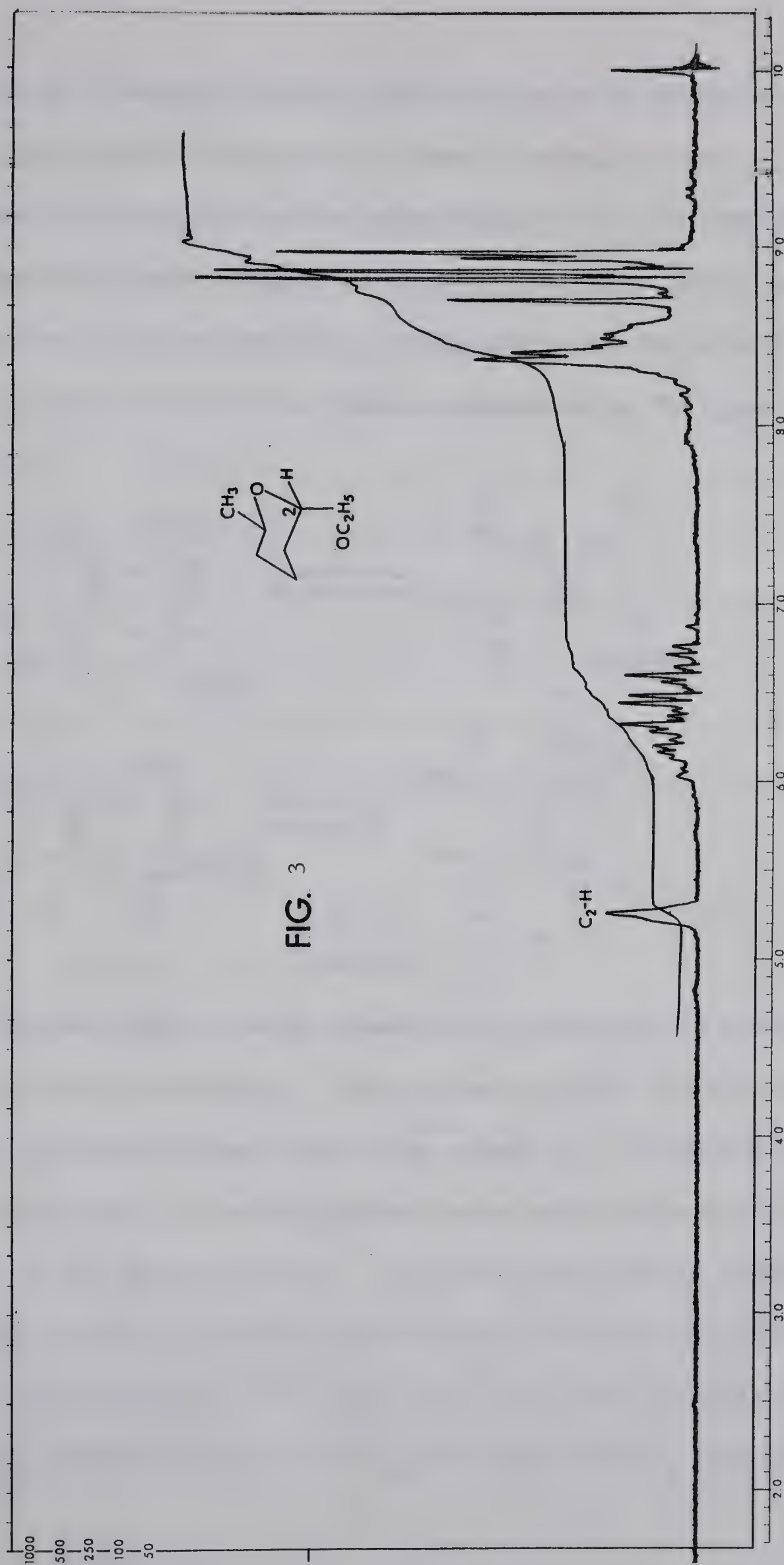


FIG. 2

N.m.r. spectrum of the cis isomer of 2-ethoxy-6-methyltetrahydropyran.



N.m.r. spectrum of the trans isomer of 2-ethoxy-6-methyltetrahydropyran.

addition an axial anomeric proton coupled with an axial proton on an adjacent carbon gives a signal with a larger coupling constant than is found when the vicinal protons are trans diequatorial. On this basis the configurations were assigned as shown in Chart 29. These assignments assume of course that the C₆ methyl group is in the equatorial position. This is the more favorable conformation for the trans isomer (Chart 30, a).

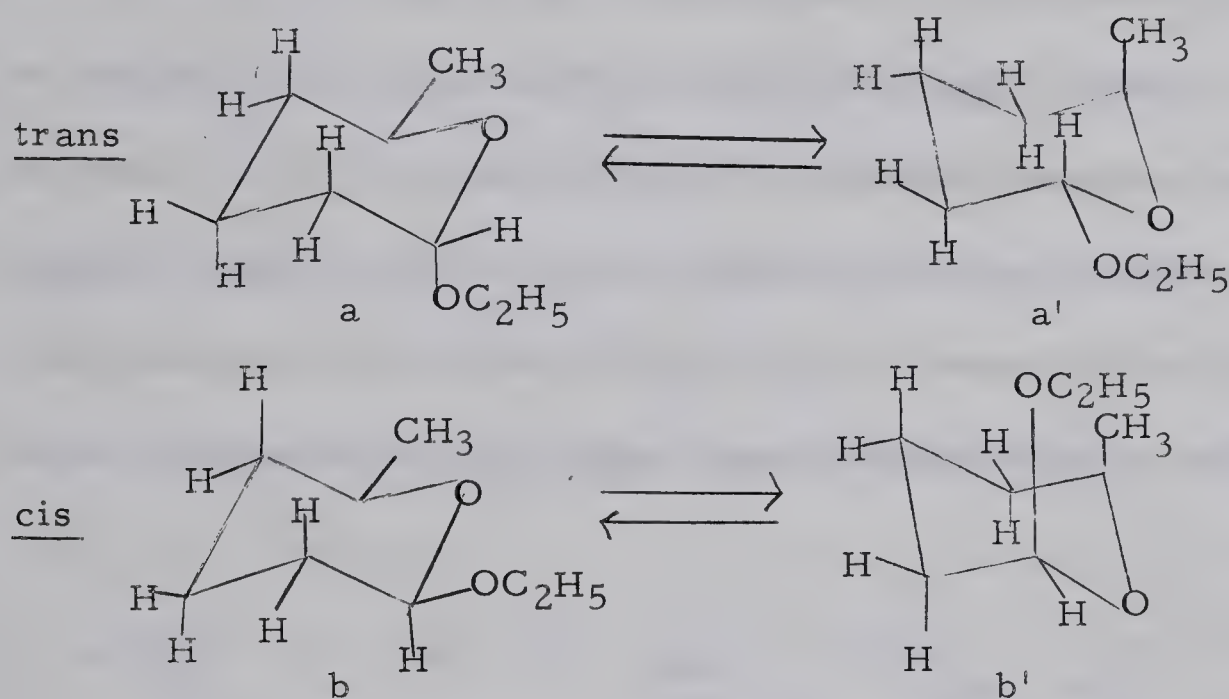


Chart 30

Both the anomeric effect and the equatorial C₆ methyl group stabilize the molecule in this conformation. The alternative "flip" conformation (Chart 30, a') would be less stable to the extent of 1.7 Kcal/mole due to the 1,3-interaction of the -CH₃ group, and as well approximately 1.4 Kcal/mole for the anomeric effect. It is very likely that the preferred conformation of the cis isomer is that shown in Chart 29, b, with the methyl group equatorial. If the cis isomer were in the alternative conformation (Chart 30, b'), the -CH₃ group and -O-C₂H₅ group would

experience a 1,3-diaxial interaction of 1.6 Kcal/mole (48) which could be largely compensated for by the anomeric effect. In addition, however, there would be one CH_3, H 1,3-diaxial interaction, often symbolized as $\text{CH}_3//\text{H}^*$, and one $\text{O}//\text{H}$ (oxygen, hydrogen 1,3-diaxial) interaction totalling 1.2 Kcal/mol as a destabilizing factor (Chart 30, b').

It is noteworthy that whereas our product 2-ethoxy-6-methyl tetrahydropyran, made from the 2-ethoxy-6-methyl-4,5-dihydropyran by catalytic reduction with H_2 , was a cis, trans, isomeric mixture in the ratio 1:1, the 6-methyl-2-isopropoxytetrahydropyran used by Eliel et al (27), prepared by an acid-catalyzed reaction of isopropyl alcohol with 6-methyl-4,5-dihydropyran (Chart 31), was obtained as an equilibrium mixture of the cis, trans isomers in the ratio of 32% to 68%.

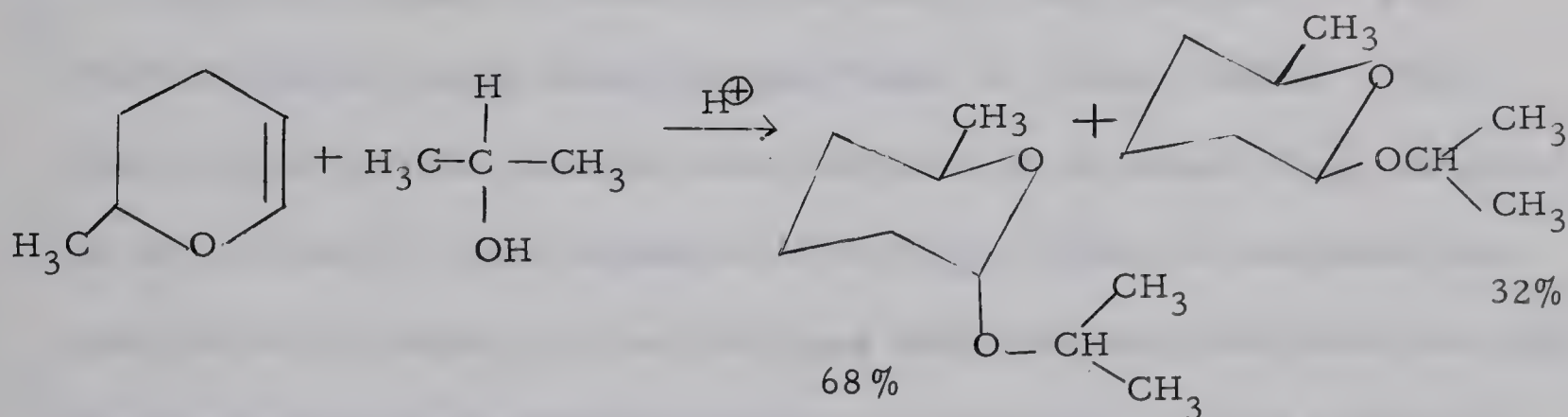


Chart 31

* A double stroke as shown is used to designate a 1,3-diaxial interaction. Similarly a single stroke designates a 1,2-gauche interaction. See R. U. Lemieux, *Molecular Rearrangements*, Vol. II, Edited by Paul de Mayo, Interscience publishers, 1964, page 709.

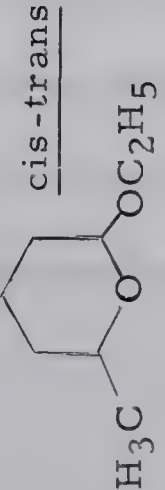
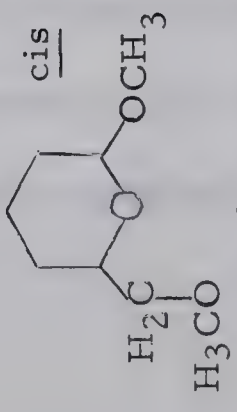
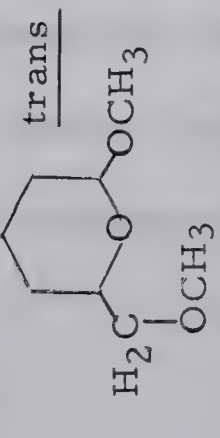
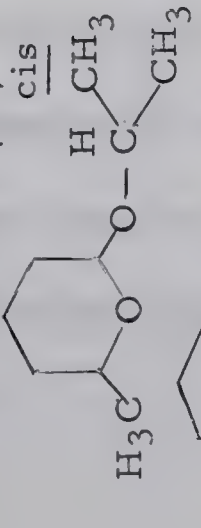
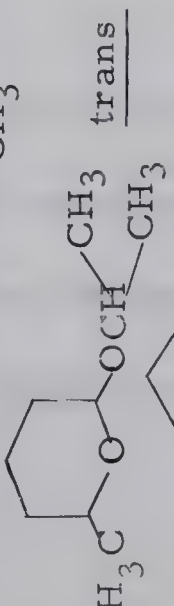
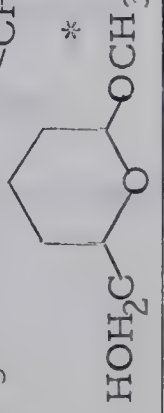
Table III shows the results of hydrogenolysis of 6-methyl-2-ethoxytetrahydropyran, as well as those for 6-methoxymethyl-2-methoxytetrahydropyran. Here again the recovery was sufficiently good to clearly demonstrate the preferred direction of reaction. Included in Table III for comparison are published results (27) for hydrogenolysis of similar compounds (items 4, 5 and 6). It is clear from Table III that a substituent at position 6 has a marked effect on the direction of cleavage. Whereas for 2-ethoxytetrahydropyran, hydrogenolysis gave 60% ring cleavage (Table I, expt. 2) the incorporation of an electron donor substituent ($-\text{CH}_3$) in position 6 gave for the cis-trans mixture of 2-ethoxy-6-methyltetrahydropyran almost exclusively (94%) side chain cleavage (Table III, expt. 1).

According to the findings reported immediately above, the reduction of both cis- and trans-6-methyl-2-isopropoxytetrahydropyran (27) gave nearly exclusively side chain cleavage (Table III, items 4 and 5). Since these results revealed no significant difference in the extent of exo cleavage for both isomers, it was decided by Eliel et al (27) that no conclusion was possible as to whether, in fact the trans (axial) isomer gives more exocyclic cleavage and the cis (equatorial) more ring cleavage". It was concluded therefore (27) that the factor responsible for this direction of cleavage was the steric interference of the methyl group at C_6 , preventing the coordination of the Lewis acid with ring oxygen.

In this argument it was assumed that rapid equilibration of the cis and trans isomers, prior to reduction, does not occur. This is in

TABLE III

Hydrogenolysis of Some 6-Substituted-2-alkoxytetrahydropyrans.

Compound	Expt. No.	Reduction Time, hr.	Extent of Reduction, %	Side Chain Cleavage, %	Ring Cleavage, %	Recovery of Material, %
 <chem>C[C@H]1CC[C@@H](OCC)O1</chem>	1	15	100	94	6	83
 <chem>COC[C@H]1CC[C@@H](OC)O1</chem>	2	17	100	40	60	78
 <chem>COC[C@@H]1CC[C@H](OC)O1</chem>	3	17	100	20	80	80
From Eliel's work (27)						
 <chem>COC[C@H]1CC[C@@H](OC(C)C)O1</chem>	4	2	-	-	2.6**	not given
 <chem>COC[C@@H]1CC[C@H](OC(C)C)O1</chem>	5	2	-	-	0.9**	not given
 <chem>COC[C@H]1CC[C@@H](CO)O1</chem>	6	3	-	100**	-	-

*Done with $\text{LiAlH}_4/\text{BF}_3$

**Given as percentage yield.

agreement with findings of Leggetter and Brown (44) concerning the reductions of the cis and trans isomers of 2,4-dimethyl-1,3-dioxolane. Isomerization during the reduction of the trans isomer was not detectable, while only a slight, if any, isomerization was noted for the cis isomer.

To assess the effect on the direction of hydrogenolysis of the polar nature of the C₆ substituent, relative to the steric hindrance of this C₆ substituent, to Lewis acid association with the ring oxygen, the compound 6-methoxymethyl-2-methoxytetrahydropyran was synthesized as illustrated in Chart 32.

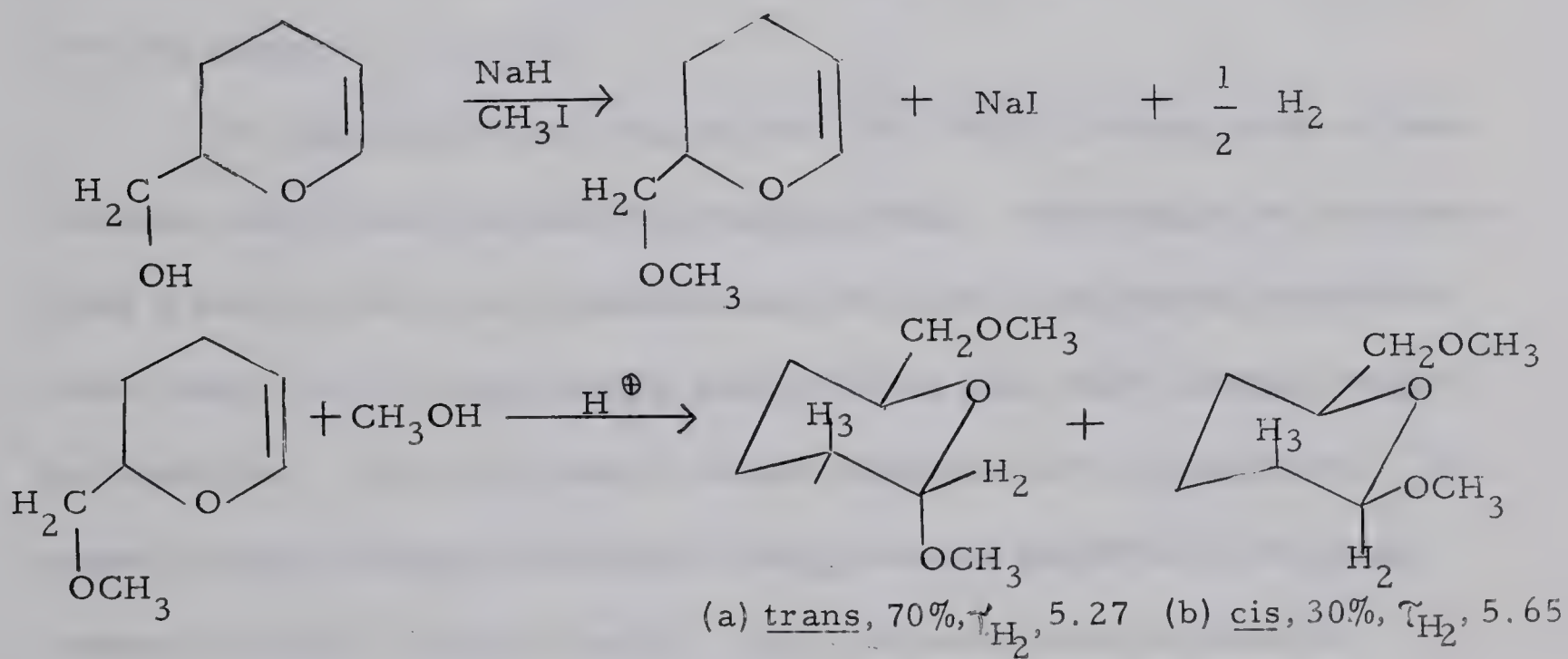
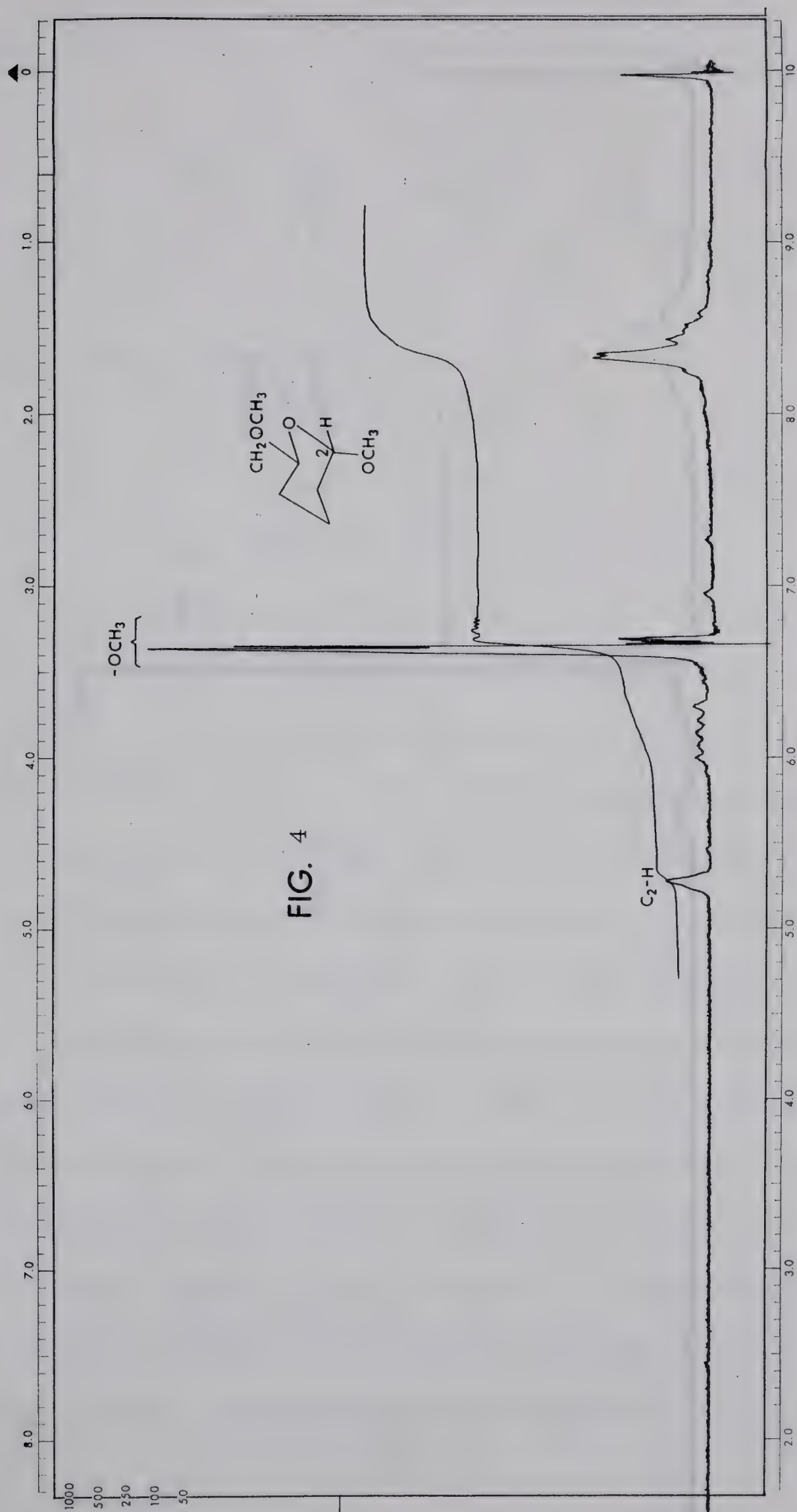


Chart 32

The two isomers in the ratio of 70% trans to 30% cis were produced when the 6-methoxymethyl-4,5-dihydropyran was treated with methanol in acid medium. These two isomers each, gave a distinct peak on the gas liquid chromatogram and were separated by preparative gas liquid chromatography.

Their configuration (Chart 32, a and b) was assigned from their n.m.r. spectra (Figs. 4 and 5). As in the case of the 6-methyl-2-ethoxy-tetrahydropyran, one of the isomers presented a broad signal at τ , 5.27 for the anomeric proton. The other isomer showed the resonance signal for the anomeric proton at τ , 5.65 and a coupling constant, $J_{2,3}$ equal to 9 c.p.s.. The same line of reasoning used for the assignment of configuration to the cis and trans isomers of the 2-ethoxy-6-methyltetrahydropyran (page 49) permitted us to assign the trans configuration to the isomer with the signal for the anomeric proton at τ , 5.27 and the cis configuration to the isomer with the signal at τ , 5.65.

We might reasonably expect the $-\text{CH}_2-\text{OCH}_3$ group to have at least the same steric effect as does the methyl group. Accordingly on hydrogenolysis if steric effects were predominant, the Lewis acid should coordinate more readily with the exo oxygen atom and thus side chain cleavage should be preferred. The experimental results showed exactly the opposite. The extent of ring cleavage was 60% for the cis isomer and 80% for the trans isomer (Table III, expts. 2 and 3). The rationale which explains the behaviour of the 2-ethoxy-6-methyltetrahydropyran and 6-methoxymethyl-2-methoxytetrahydropyran takes into consideration the relative inductive effects of the methyl and methoxymethyl groups at carbon 6 and the concept of the formation of a resonance-stabilized oxocarbenium ion as an intermediate. We can say that this carbonium ion is product determining. This resonance-stabilized oxocarbenium ion may arise by (a): cleavage of the



N.m.r. spectrum of the trans isomer of 6-methoxymethyl-2-methoxytetrahydropyran.

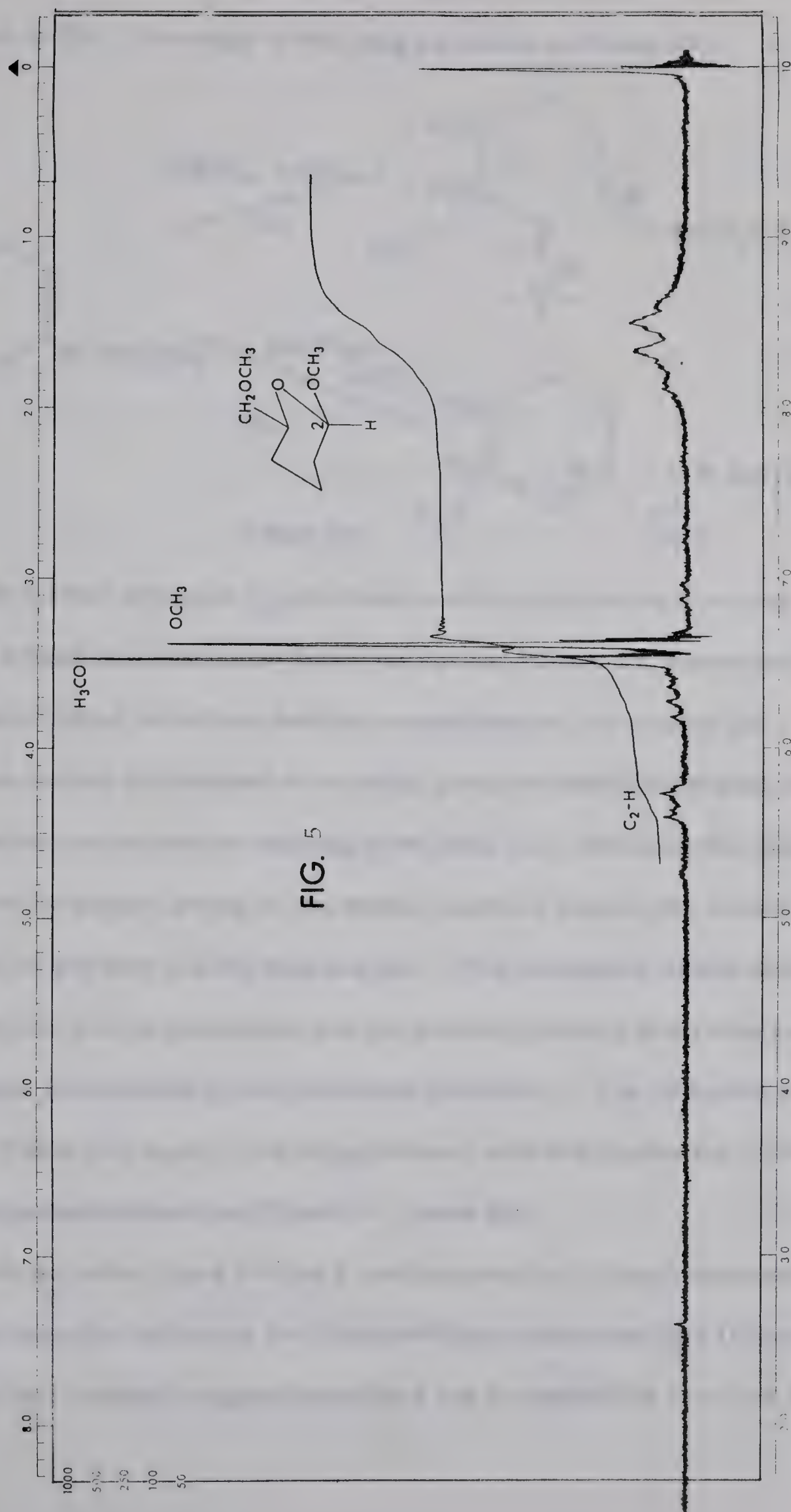
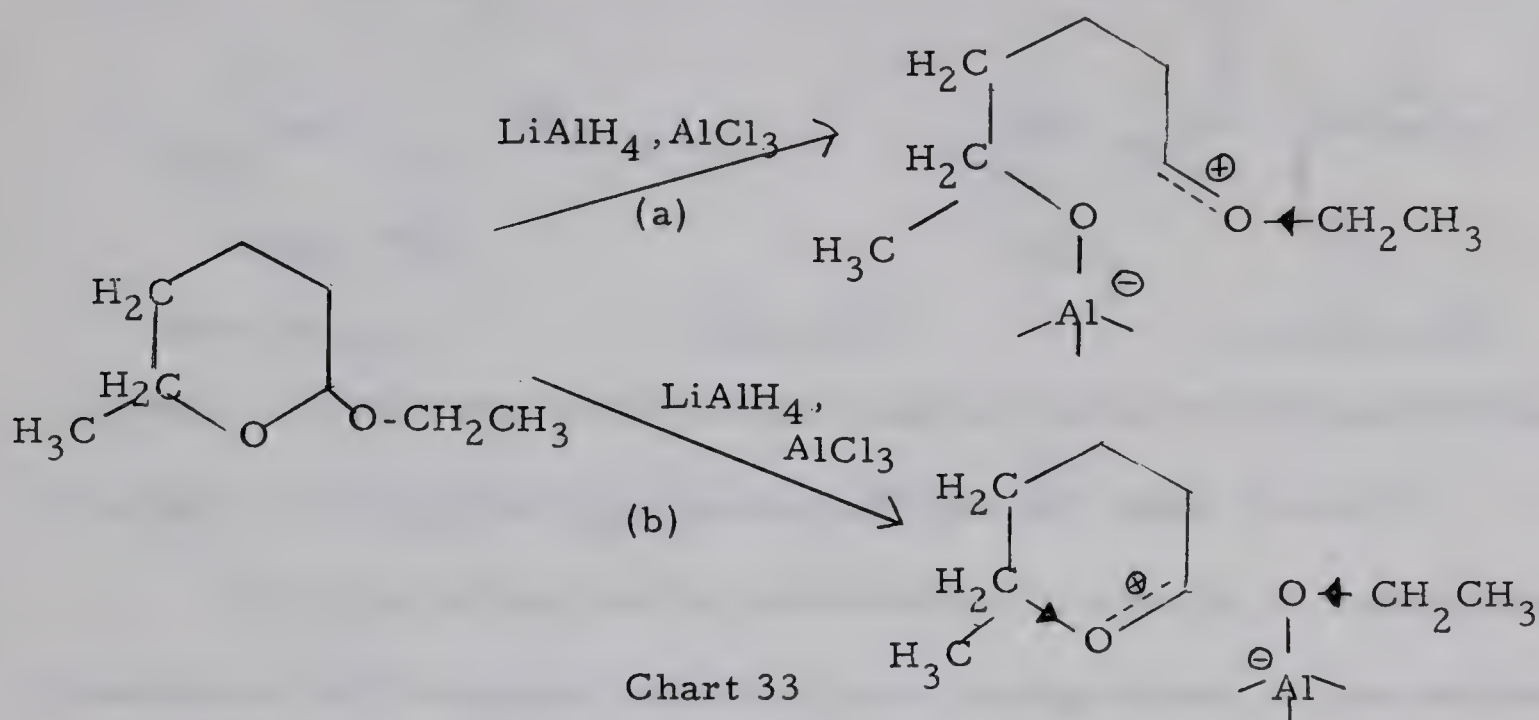


FIG. 5

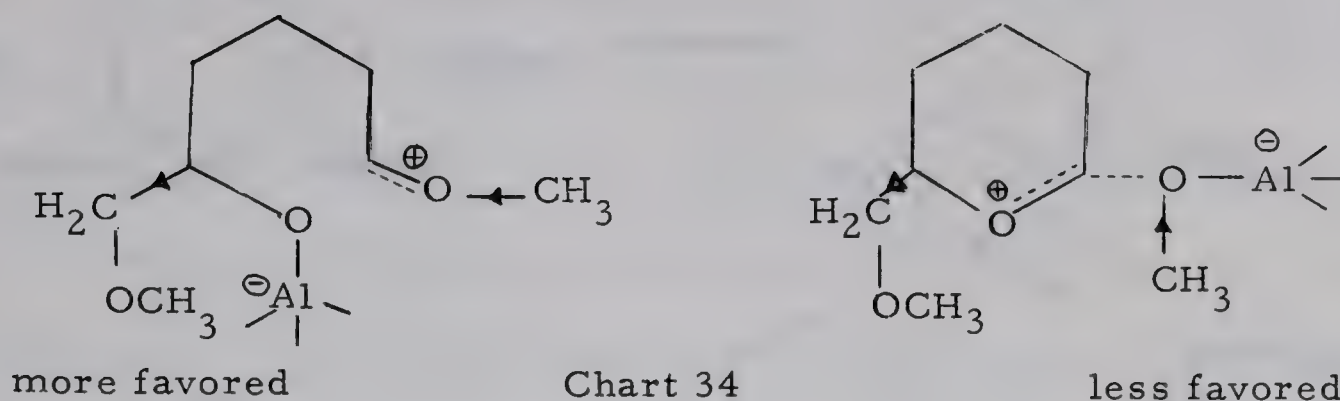
N.m.r. spectrum of the cis isomer of 6-methoxymethyl-2-methoxytetrahydropyran.

side chain or (b) : cleavage of the ring as shown in Chart 33.



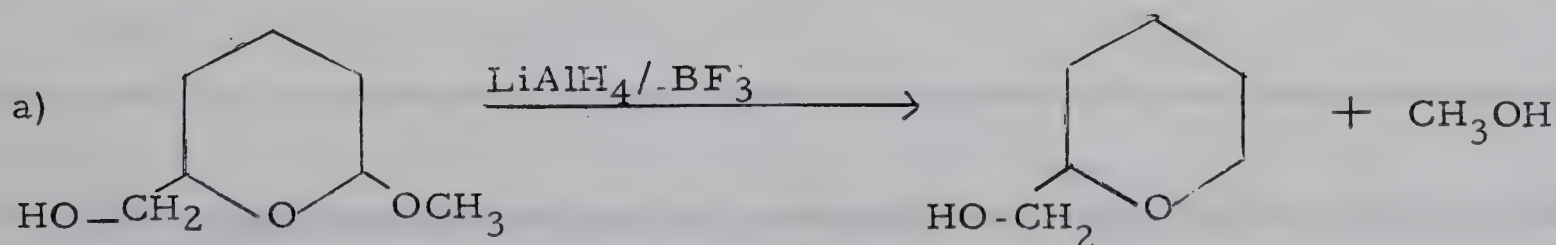
A methyl group at C₆ produces a structure having the ring oxygen attached to what amounts to an isopropyl group (Chart 33, heavy type) in both the original structure and the oxocarbenium ion of path (b). The exo oxygen in turn is attached to an ethyl group in both the original molecule and in the oxocarbenium ion arising from path (a). Since of the two alkyl groups, the isopropyl group is the better electron donor, the stabilizing effect will be greater via (b) than via (a). The formation of the more stable carbonium ion will be preferred and the product arising from this ion will be the major constituent of the reduction products. The 94% side chain cleavage (Table III, expt. 1) is in agreement with the formation of the preferred oxocarbenium ion (Chart 33, route (b)).

On the other hand for the 6-methoxymethyl-2-methoxytetrahydropyran, we have the following two intermediate carbonium ions (Chart 34). It is clear that the more highly stabilized ion is that which involves ring



cleavage, in agreement with the experimental finding of 60% and 80% ring cleavage for the cis and trans isomers (Table III, expts. 2 and 3).

It is interesting that the unmethylated compound, 6-hydroxymethyl-2-methoxytetrahydropyran was found upon hydrogenolysis to give exclusively 2-hydroxymethyltetrahydropyran (27) (Chart 35, a). This is the product arising from side chain cleavage and is the reverse of what is obtained from hydrogenolysis of the methylated compound. The course of reaction had been explained (27) in terms of steric interference by the $-CH_2OH$ group to Lewis acid association with the ring oxygen. In view of the results obtained in the present work on the hydrogenolysis of 6-methoxymethyl-2-methoxytetrahydropyran this appears unlikely since one would expect that the methoxymethyl group would be at least as bulky as the hydroxymethyl group, and give the same preferred direction of cleavage, a fact not observed. One might explain the exclusive exo cleavage of the 6-hydroxymethyl compound by the initial formation of the boron salt of the alcohol moiety (Chart 35, b).



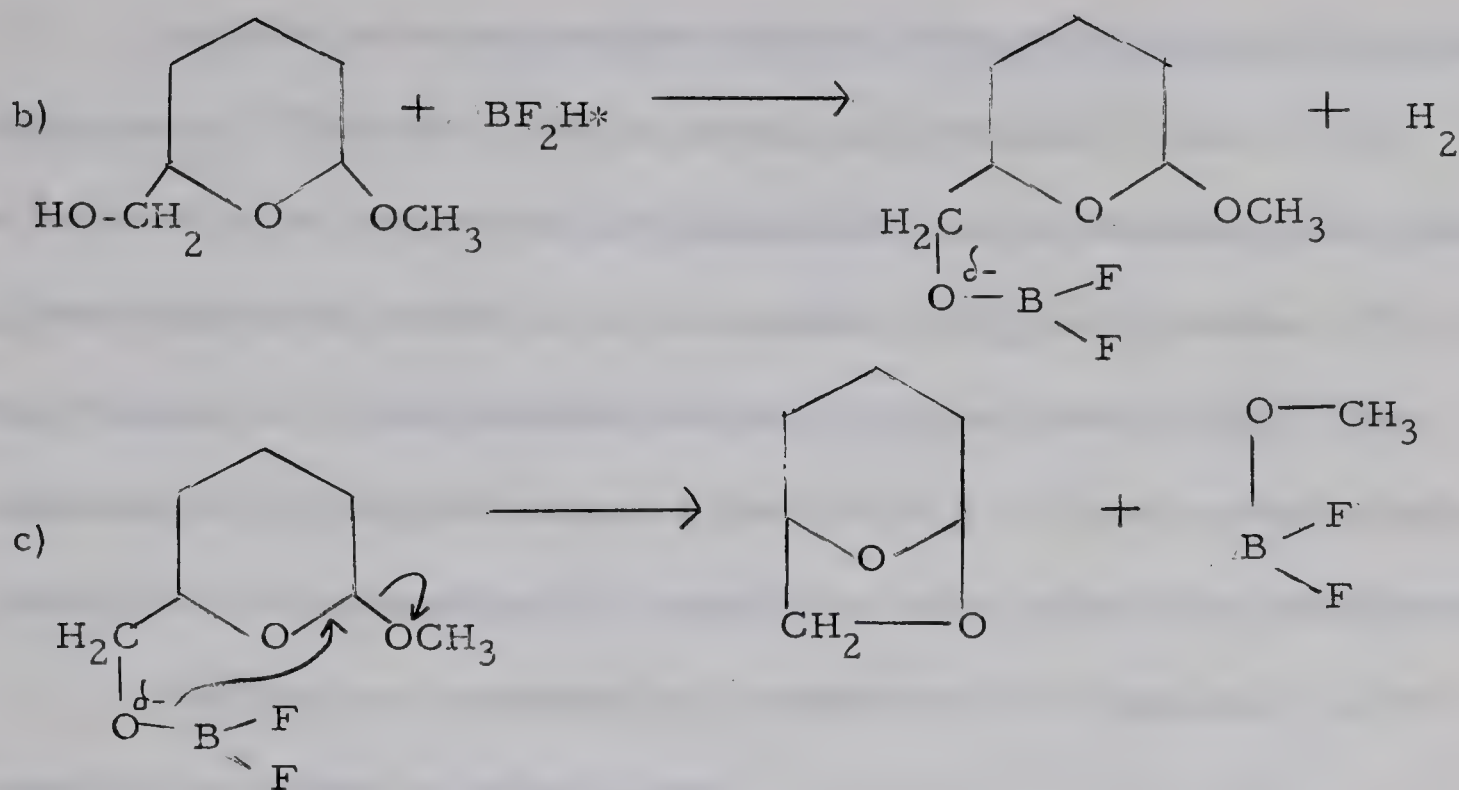
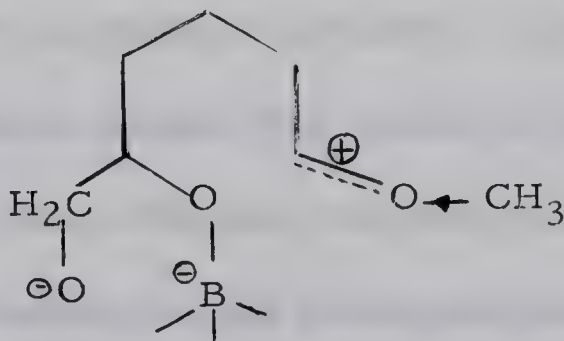
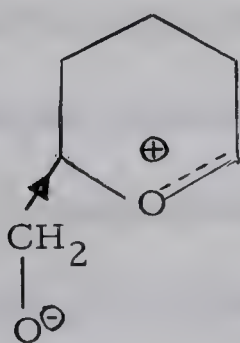


Chart 35

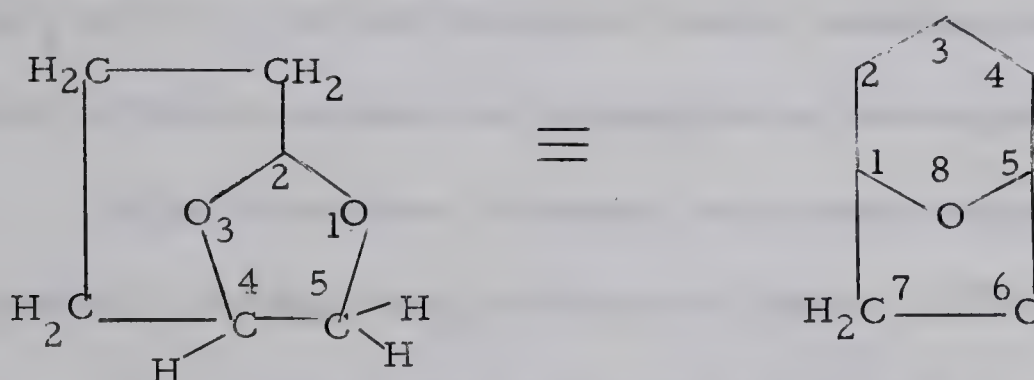
This anion $R-CH_2O^-$ is no longer electron withdrawing and hence might in fact stabilize the oxocarbenium ion arising from ring retention, to a greater extent than does the methyl group for the alternative oxocarbenium ion (see below). As well, the incipient bulk of the ion pair $CH_2O^{\ominus}BF_2$ (Chart 35, b) might in addition hinder approach of the Lewis acid to the ring oxygen.



* This is presumably the species produced, according to the ratio of $LiAlH_4$ to BF_3 employed by Eliel et al (27).

An alternative explanation which is attractive, is based upon polar effects only. This also involves initial salt formation (Chart 35, b). This is followed by an intramolecular displacement of the methoxy group (Chart 35, c) resulting in the formation of 6,8-dioxabicyclo[3.2.1]octane. This is then reduced to 2-hydroxymethyltetrahydropyran (Chart 35, a). The reduction of this bicyclo compound, exclusively to 2-hydroxymethyltetrahydropyran can be explained in terms of the polar effect discussed previously.

This bicyclo compound is a substituted 1,3-dioxolane. If its structure is written as shown below;



and for reasons of convenience, we number the dioxolane portion in the usual way (left structure) it is seen that O₃ has the equivalent of an ethyl group attached to it while O₁ is attached to a methyl equivalent. Upon hydrogenolysis this substance should produce largely the product arising from C₂—O₁ bond cleavage. In favor of this is the fact that pure 6,8-dioxabicyclo[3.2.1]octane produces exclusively (upon hydrogenolysis) 2-hydroxymethyltetrahydropyran (27).

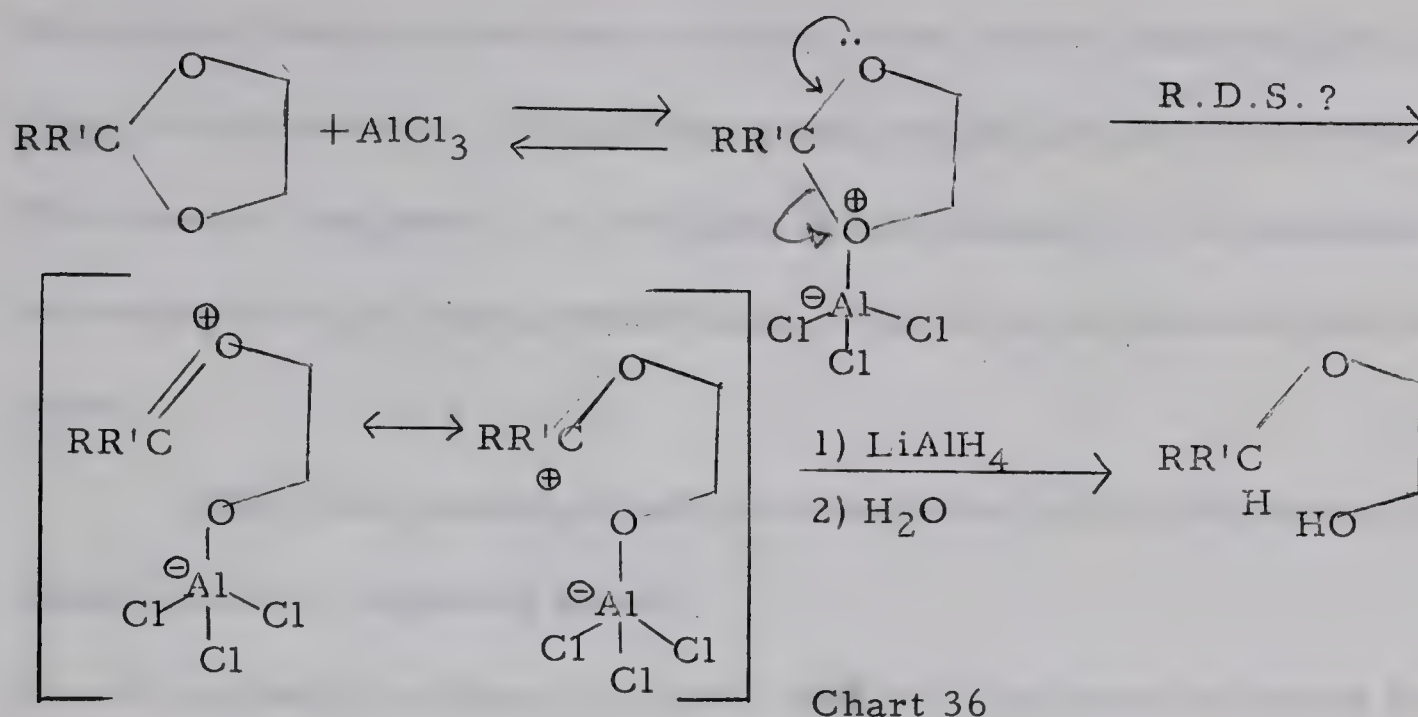
VII. Mechanistic Interpretation of the Hydrogenolysis of Acetals and Ketals by the Mixed Reagent.

From the material presented this far , we believe that it would be instructive to present now a mechanistic interpretation concerning the hydrogenolysis of the acetals and ketals. This also will permit a better understanding of the following sections.

To this date no kinetic studies have been reported for the reaction of the mixed reagent with acetals or ketals. The recent work by Ashby and Prather (32) on the nature of the reducing species by mixtures of LiAlH_4 and AlCl_3 should stimulate kinetic investigations. In fact an attempt in this direction is at present under investigation in our laboratory.

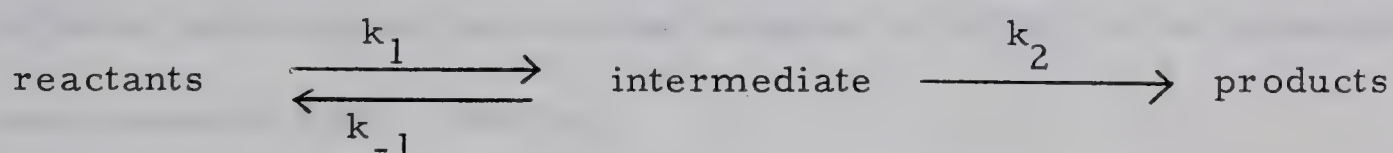
Suggestions have , however , been made concerning likely mechanistic pathways (see Introduction, pages 13-18).

Eliel (15) proposed the attack by LiAlH_4 on the complex formed by coordination of the Lewis acid with the acetal or ketal as shown in Chart 36. Formation of a stabilized carbonium ion was believed to be a part of this mechanistic route. Work in our laboratory (1) has supported the view that carbonium ion formation is involved in the rate-determining step , since when group R and R' are electron donors , the reaction is enhanced , while if R and R' are electron withdrawing groups the reaction is retarded. The marked similarity of the polar effects of C_2 substituents in acetal hydrogenolysis to those obtained from kinetic studies of acid-catalyzed hydrolysis of similarly substituted acetals , in which carbonium



ion formation is considered to be rate controlling, adds further weight to our view.

However two kinetic interpretations have been proposed (27) for the scheme portrayed in Chart 36. The first implies the expression



where $k_2 \gg k_{-1}$. This is tantamount to the idea of oxocarbenium ion formation as the rate-controlling step. The second interpretation is that $k_2 \ll k_{-1}$, and accordingly, attack by hydride on the carbonium ion is rate controlling.

Work done by Leggetter and Brown (44) provided information in favor of the first interpretation. Partial hydrogenolysis of either cis- or trans-2,4-dimethyl-1,3-dioxolane gave reduction products along with starting material which had suffered negligible or no isomerization. Under identical conditions AlCl_3 alone gave extensive isomerization. If

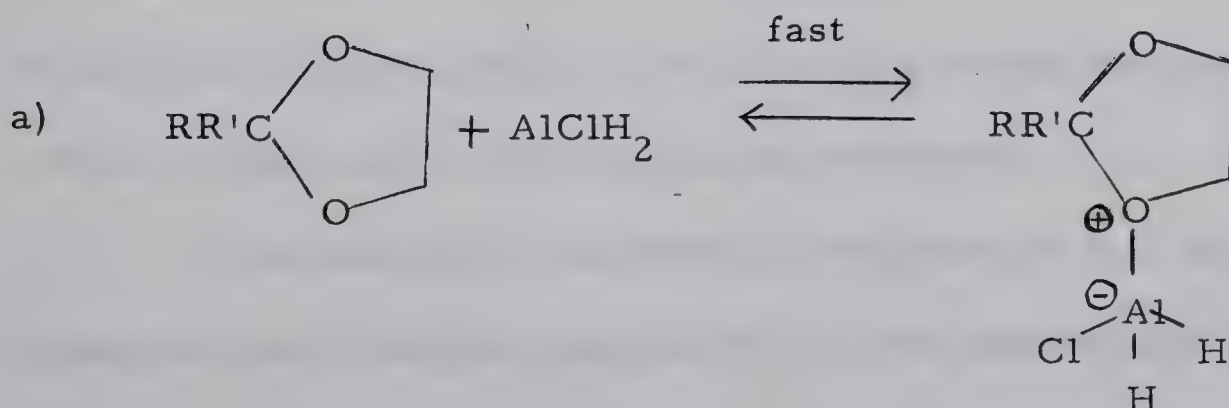
the second interpretation were correct, then isomerization of cis- or trans-2,4-dimethyl-1,3-dioxolane would indeed have been observed.

This was not the case. In the light of this evidence it is reasonable to assume that the first interpretation is more in accordance with the facts.

The work presented and discussed thus far in this thesis has established the following points.

- 1) An equimolar mixture of LiAlH_4 and AlCl_3 in ether produces the reducing species AlClH_2 . Neither AlCl_3 nor LiAlH_4 are present in the ethereal solution after the mixture has been made.
- 2) The AlClH_2 , once formed, is stable and does not disproportionate under our conditions. This is shown by the observation in the infrared spectrum of the ethereal solution of AlClH_2 of the absorption band characteristic of AlClH_2 .

Consequently we can postulate as the first step in the reaction, a coordination of the AlClH_2 with either of the two oxygen atoms of the acetal or ketal. This association is considered to be fast and reversible (Chart 37, a).



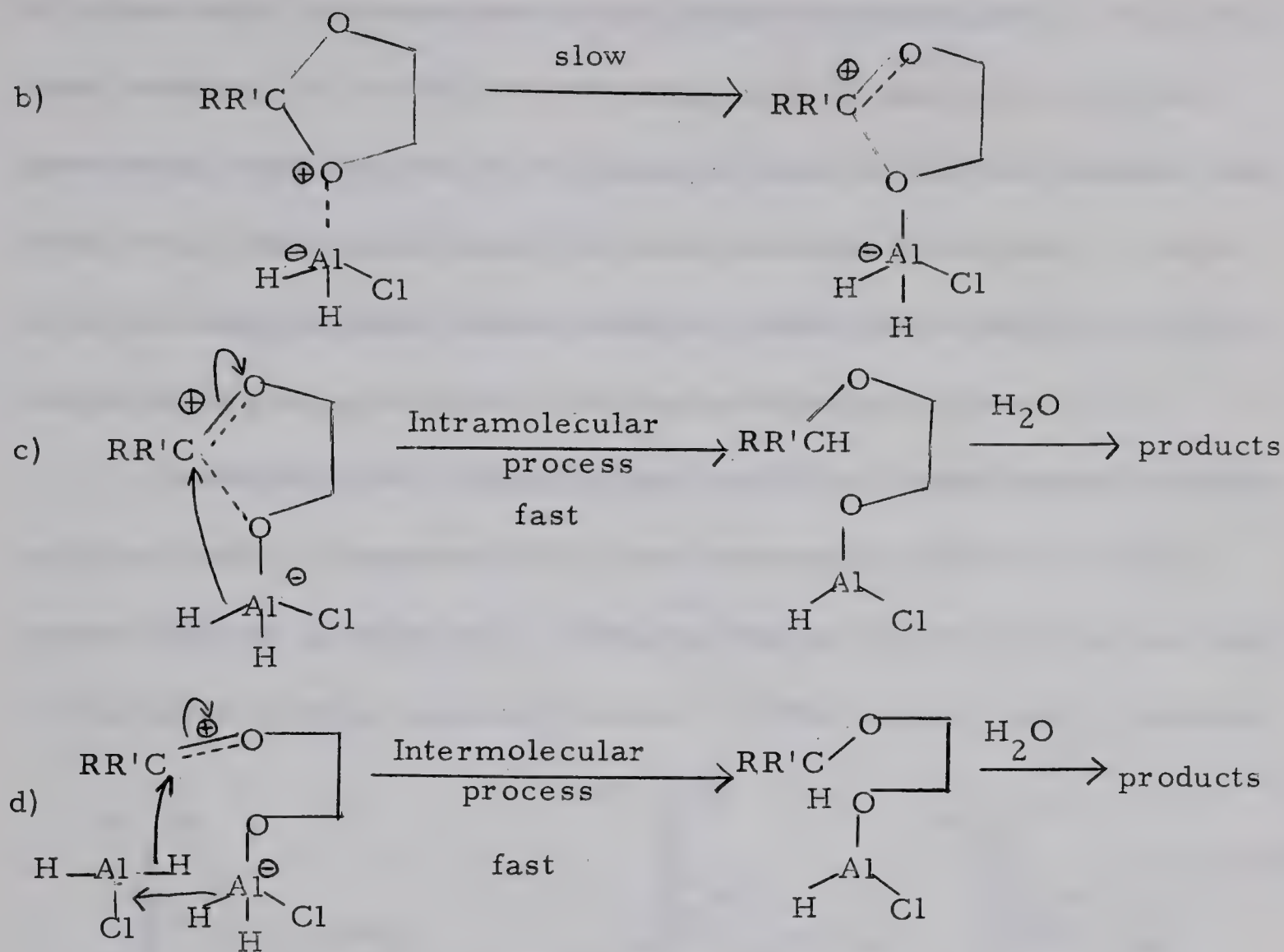


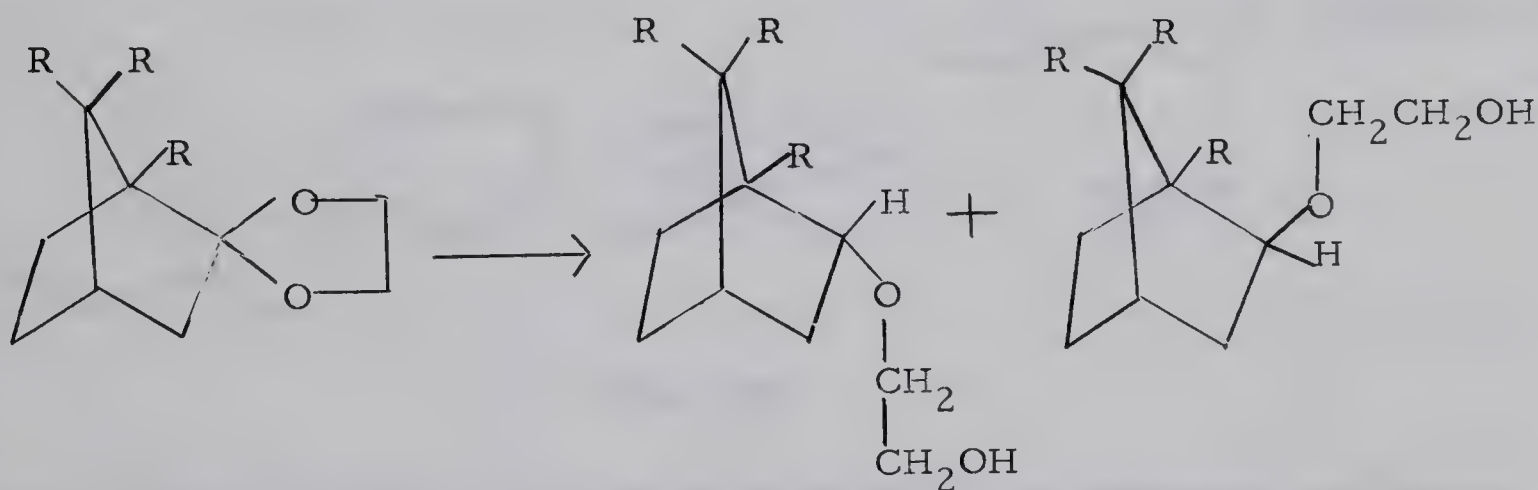
Chart 37

Since we can consider AlClH_2 to be a strong Lewis acid (34), the resulting complex could then form a carbonium ion, or at least a species possessing considerable carbonium ion character (Chart 37, b). This formation is the slow rate-controlling step. The carbonium ion rapidly receives a hydride ion, either by an intramolecular (Chart 37, c) or by an intermolecular process (Chart 37, d). No decision as yet can be made as to which process, (c) or (d), is actually preferred.

The possibility that hydride reduction occurs via a four-centre transition state has been suggested by Ashby and Prather (32). Process

(c) above might accommodate a four-center transition state. But C-O bond breaking, or partial bond breaking, with formation of a species possessing some carbonium ion character must be a prime requisite and must occur before significant C-H bond formation takes place, in order to accommodate the polar effects noted for electron donating and electron withdrawing groups attached to the carbon atom so involved.

A recent report (49) of the reaction of the mixed reagent with the ethylene ketals of camphor ($R=CH_3$) and norcamphor ($R=H$) (Chart 38) showed that the proportion of products obtained (endo/exo) was explicable on the basis of steric approach control. Either a four-center transition



$R = H$, 100%

0%

$R = CH_3$, 22%

78%

Chart 38

state or intermediate carbonium formation might explain the results.

Some decision can be made as to whether the reaction proceeds by way of a four-center transition state or by prior formation of a carbonium ion by considering the results obtained from the hydrogenolysis

of 4-t-butylcyclohexanone ethylene hemithioketal by $\text{LiAlH}_4\text{-AlCl}_3$ (17, 18). Both isomers gave only one compound (Chart 39), the trans-4-t-butylcyclohexyl β -hydroxyethyl ether in high yield (86-92%). No evidence for the presence of the cis isomer was found.

This result can be explained nicely by the mechanistic scheme suggested below. A significant point which must be kept in mind is that these oxathiolanes cleave only at the C-O bond. No evidence of cleavage

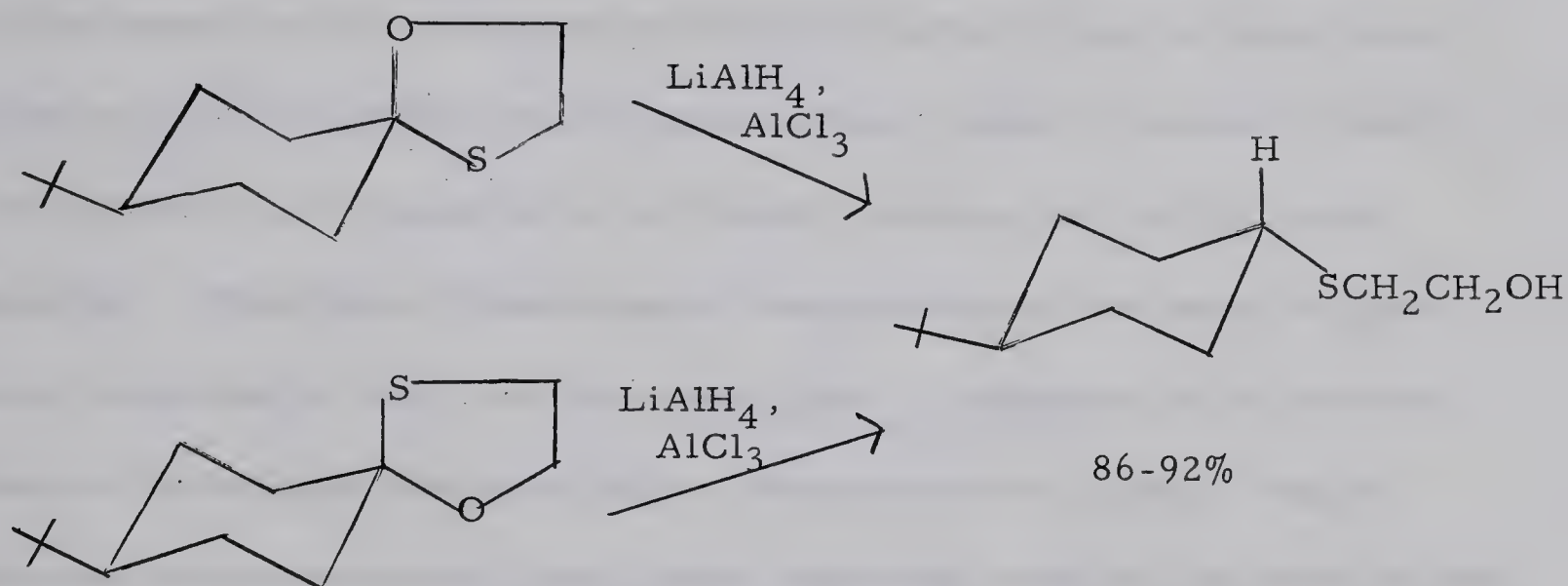
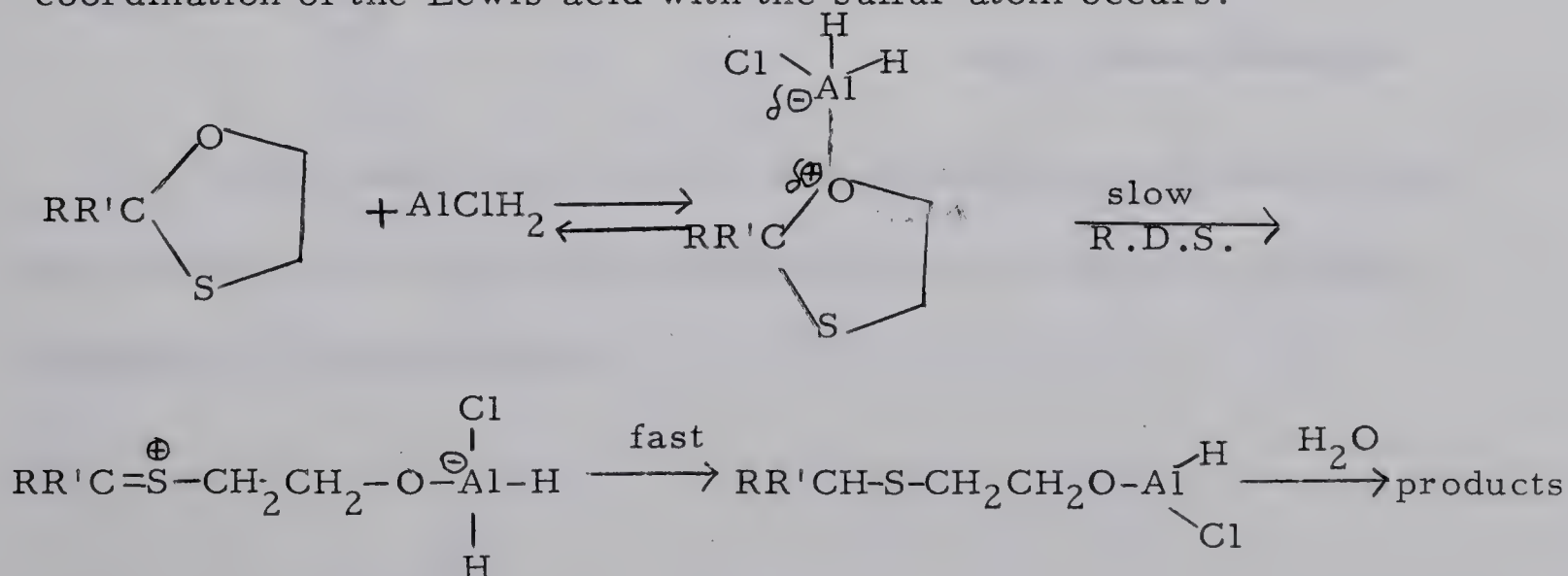
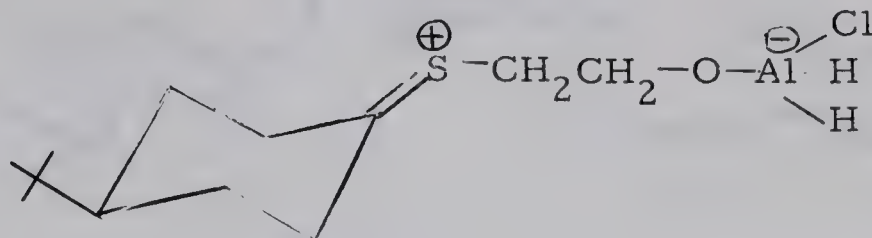


Chart 39

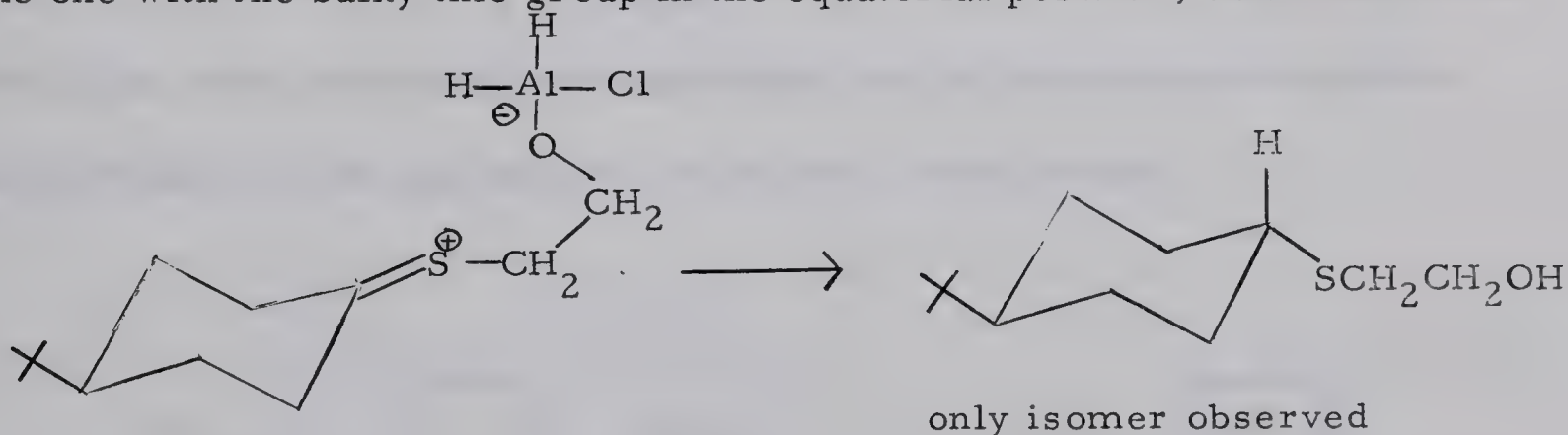
of the C-S bond has been found either by Eliel (17) or Leggetter and Brown (18). This can be interpreted as evidence that little or no effective coordination of the Lewis acid with the sulfur atom occurs.



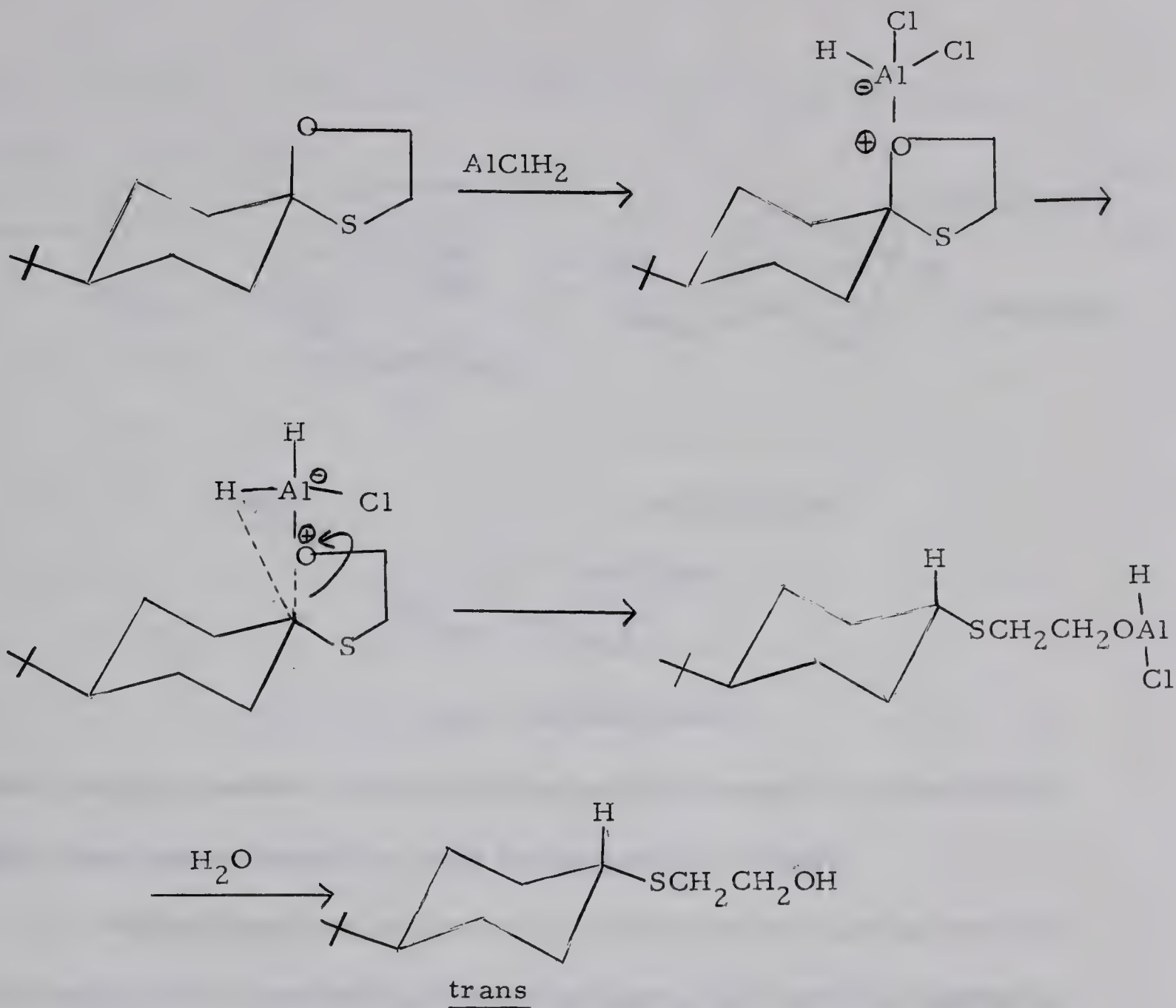
In the specific case under consideration here, the carbonium ion formed will be,



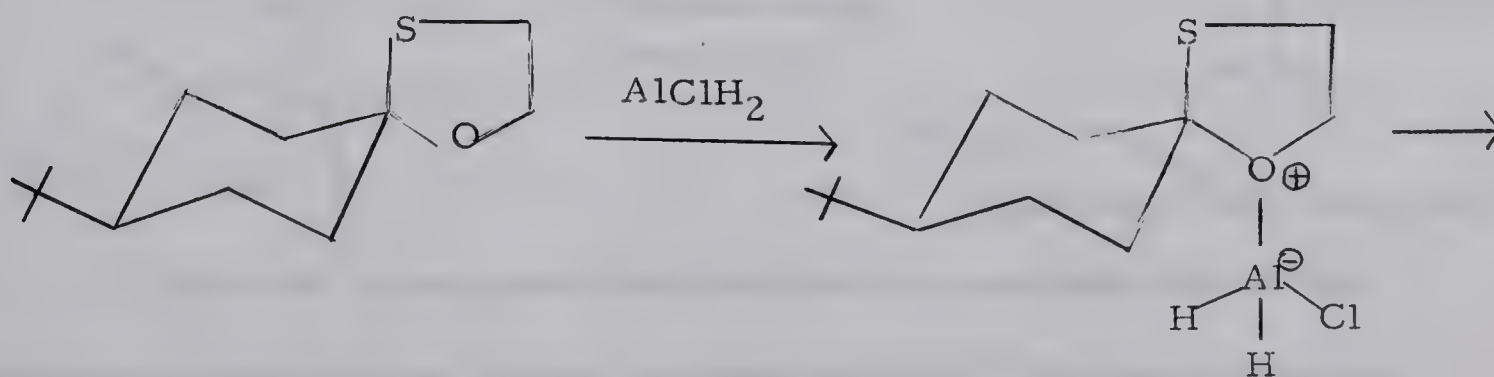
and this could be considered a common intermediate for both isomers portrayed in Chart 39. We discard the possibility of rapid equilibration of the isomers with consequent preferred reduction of one of them, since Eliel et al (17) found that equilibration of these isomers proceeds slowly, (equilibrium was obtained after a 24 hour treatment with BF_3 in ether solution). Reaction of these types of compounds with the mixed reagent were completed in less than three hours (48). Reduction of the sulfocar-
bonium ion will give the more stable compound as the product, that is, the one with the bulky thio group in the equatorial position, as shown below.

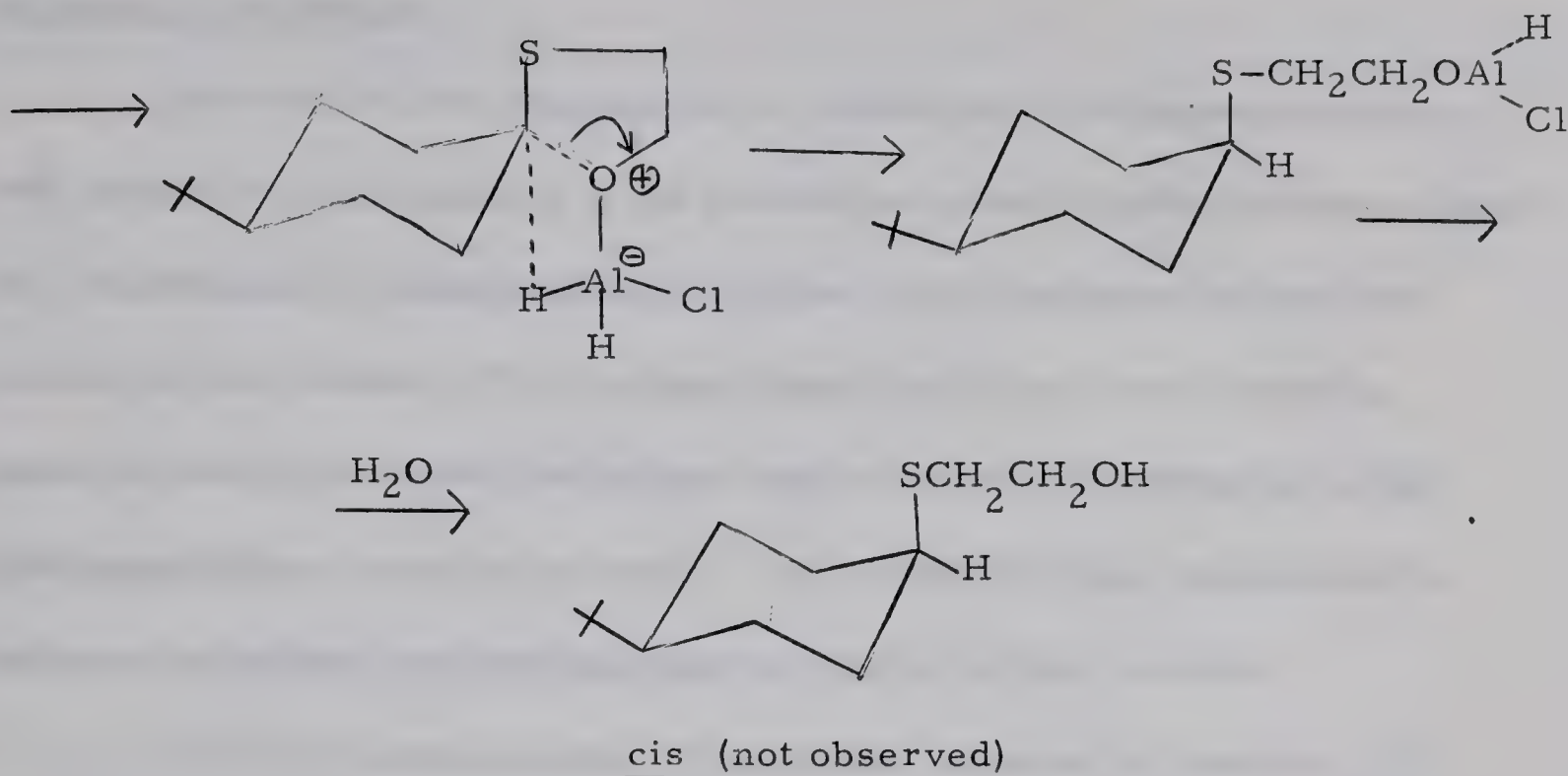


On the other hand if we try to explain the results obtained, by the concept of the four-centre transition state, we have the following situation for the one isomer.



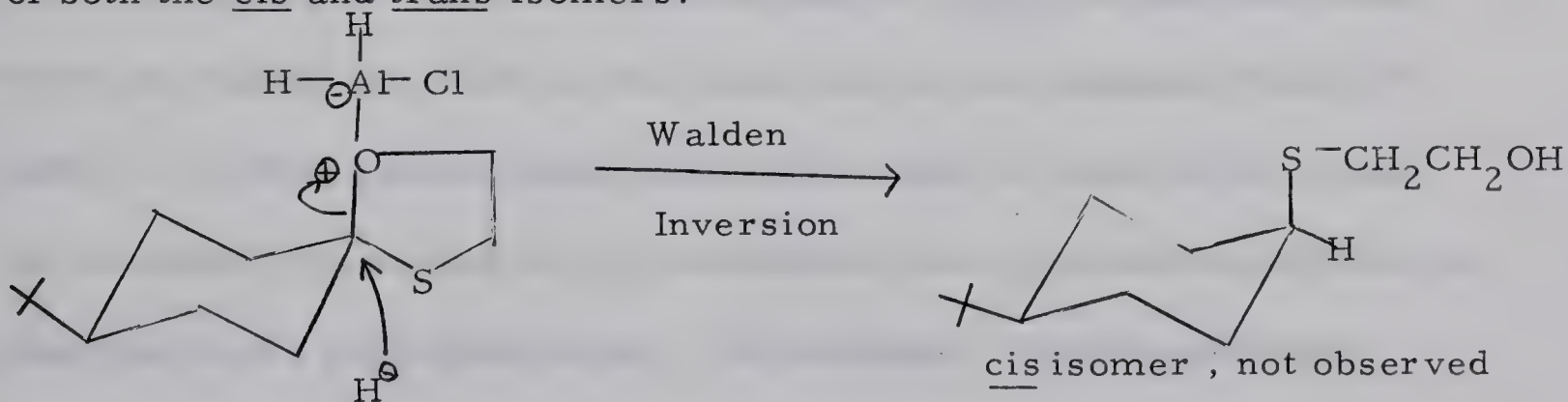
While the other isomer by hydrogenolysis via the four-centre transition state would give the cis isomer, as the only logical result:





Since the trans isomer is the exclusive product formed in a yield of 86-92% a four-center transition state mechanism is unlikely.

We still have the possibility of a bimolecular reaction between the complex of the hemithioketal with the Lewis acid and the hydride ion. But if this were the mechanistic pathway we should observe the formation of both the cis and trans isomers.



From the above considerations we can postulate that in the reductions of acetals and ketals, at least with AlCl_2H , the carbonium ion mechanism is the more probable one.

VIII. Relevant Information Pertaining to Hydrolysis and Hydrogenolysis of Acetals and Ketals.

Material in this discussion is considered to be appropriate and will aid in the consideration of the problems concerning the hydrogenolysis of 3-substituted-2-alkoxytetrahydropyrans to be discussed in the later section of this thesis. The findings described below have a bearing upon our belief that inductive effects are of primary importance in the hydrogenolysis of acetals or ketals. In relation to this, the similarity between hydrolysis and hydrogenolysis should be kept in mind.

We will examine some of the results obtained by Leutner (21), Ceder (25) and Salomaa (26) in their kinetic studies of the hydrolysis of cyclic acetals and ketals.

A. Activation Energies.

According to Ceder (25), the hydrolysis of acyclic acetals is characterized by an energy of activation of about 25 Kcal/mole. The activation energies reported by Ceder for the cyclic acetals and ketals which he studied are close to this value only in one instance (Table IV, item 1). In three of the cases (Table IV, items 2, 4 and 6) the values are somewhat lower, but for the remainder there is a greater difference from the figure of 25 Kcal/mole. He concluded "that the energy of activation is more dependent on the nature of the oxo compound than of the acetal character". On the other hand if we examine the activation energies reported by Salomaa (26) for the hydrolysis of several

TABLE IV

Energies of activation and rates of hydrolysis of some dioxanes and diololanes.

Compound	Ea Kcal/mole	k at 30°C min ⁻¹	10 ⁴ k at 25°C 1 mole ⁻¹ sec ⁻¹	k at 25°C min ⁻¹
1) 1,3-dioxolane	27.1	5.9 · 10 ⁻⁴		
2) 2,2-dimethyl-1,3-dioxane	19.8	322		
3) 2-phenyl-1,3-dioxolane	14.8	159		
4) 2-phenyl-1,3-dioxane	20.9	46.2		
5) 2-methyl-2-phenyl-1,3-dioxolane	17.5	44.8		
6) 2-methyl-2-phenyl-1,3-dioxane	19.3	265		
7) 2-styryl-1,3-dioxolane	12.7	1955		
8) 2-styryl-1,3-dioxane	14.7	647		
9) 2,2-diphenyl-1,3-dioxolane	17.2	4.92		
10) 2,2-diphenyl-1,3-dioxane	17.4	19.3		
11) 1,3-dioxolane	25.48		0.0265	
12) 2-methyl-1,3-dioxolane	22.25		136	
13) 2,2-dimethyl-1,3-dioxolane	21.54		1440	
14) 2,2,4-trimethyl-1,3-dioxolane	20.70		1460	
15) 2,4-dimethyl-1,3-dioxolane, <u>cis</u>	20.66		195	
16) 2,4-dimethyl-1,3-dioxolane, <u>trans</u>	20.95		50.7	
17) 2,4,4,5,5-pentamethyl-1,3-dioxolane	20.63		18.9	
18) 1,3-dioxane	-			5 × 10 ⁻⁵
19) 2-methyl-1,3-dioxane	-			0.13
20) 2,2-methyl-1,3-dioxane	-			338

*Taken from the work by Ceder (25).

**Taken from the work by Salomaa (26).

***Taken from the work by Leutner (20, 21).

1,3-dioxolanes, and compare them with those reported by Ceder, we observe that with a few exceptions most of the values are close to the figure of 20 Kcal/mole (Table IV, items 11-17).

A similar situation is observed in the hydrolysis of several glycopyranosides (50) where all the values are close to the figure 30 Kcal/mole.

We see that each set of substances, the acyclic and cyclic acetals and the glycopyranosides, appears to have a characteristic value of the activation energy. This can be interpreted as evidence of the similarity in the pathway of hydrolysis followed by these classes of substances. The differences observed are probably the result of differences in structure.

B. Inductive Effects and Steric Effects.

(1) If we now examine entries 18, 19 and 20 in Table IV, we see that for the 1,3-dioxanes, there is an increase by a factor of 2.6×10^3 in the speed of hydrolysis, due to the introduction of the first $-CH_3$ group on C_2 . The second $-CH_3$ group increases the speed again by approximately the same factor (2.6×10^3). This agrees well with the results found by Taft and Kreevoy (19) in their study of the effects of alkyl substituents on the "central carbon" of diethyl acetals on the hydrolysis rates of these acetals. This is shown in Table V.

TABLE V

Rates of Hydrolysis of Some Diethyl Acetals. *

Compound	$k(1 \text{ mole}^{-1} \text{ sec}^{-1})$ at 25°C	Δk
$\begin{array}{c} \text{OC}_2\text{H}_5 \\ \diagup \\ \text{H}_2\text{C} \\ \diagdown \\ \text{OC}_2\text{H}_5 \end{array}$	4.3×10^{-5}	5.5×10^3
$\begin{array}{c} \text{H} \quad \text{OC}_2\text{H}_5 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H}_3\text{C} \quad \text{OC}_2\text{H}_5 \end{array}$	0.248	
$\begin{array}{c} \text{H}_3\text{C} \quad \text{OC}_2\text{H}_5 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{H}_3\text{C} \quad \text{OC}_2\text{H}_5 \end{array}$	752	3.0×10^3

*Taken from the work of Taft and Kreevoy (19).

Also in agreement with these values are those cited by Ingold (51) from the work of Skrabal (52) concerning the hydrolysis of the compounds obtained from the reaction of pentaerythritol with formaldehyde, acetaldehyde and acetone. Each methyl substituent attached to the C_2 position (anomeric carbon) increased the speed by a factor of about $10^{3.5}$.

On the other hand, the dioxolanes show for the introduction of the first $-\text{CH}_3$ group on C_2 an increase in the rate by a factor of $10^{3.5}$ as expected. But introduction of a second methyl group on C_2 increases the rate by a factor of only 10^1 (Table IV, compare items 11, 12, 13).

This was explained by Salomaa in terms of steric interference between the methyl group on C_2 and the dioxolane ring, as shown below (Chart 40a).

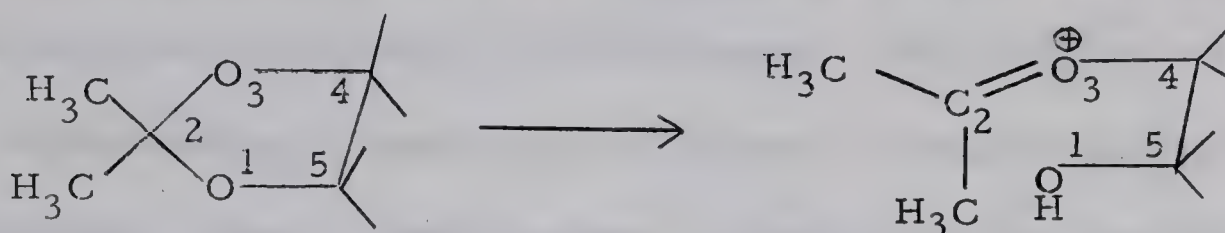


Chart 40a

According to Salomaa's interpretation (26), when the intermediate carbonium ion is formed, one of the C_2 - CH_3 bonds has to bend towards the ring in order that the two methyl groups and C_2 , O_3 and C_4 all achieve coplanarity. This creates some degree of steric strain that would account for the decrease in reactivity.

However, as can be seen by a comparison with the structure of 2,2-dimethyl-1,3-dioxane (Chart 40b), a similar steric situation is found in the six-membered ring acetals. Yet, the increase of speed is additive (Table IV, items 18-20). Because of this inconsistency we believe that it is doubtful that the 'steric effects' suggested by Salomaa are responsible for this anomaly.

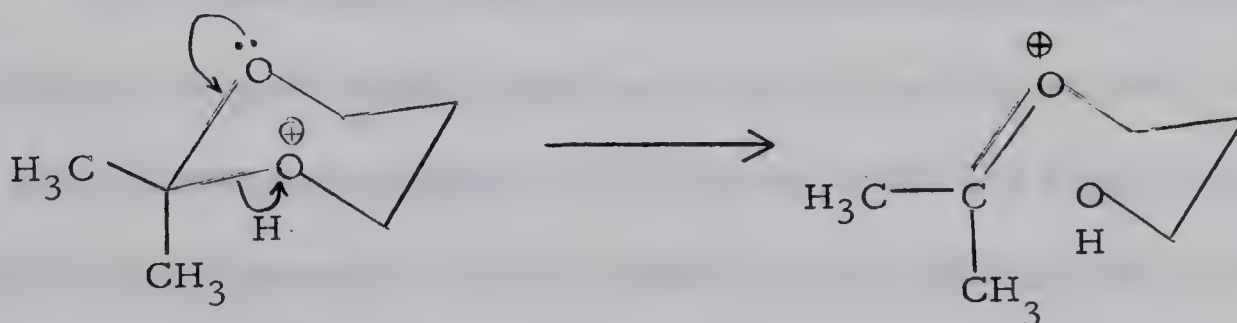
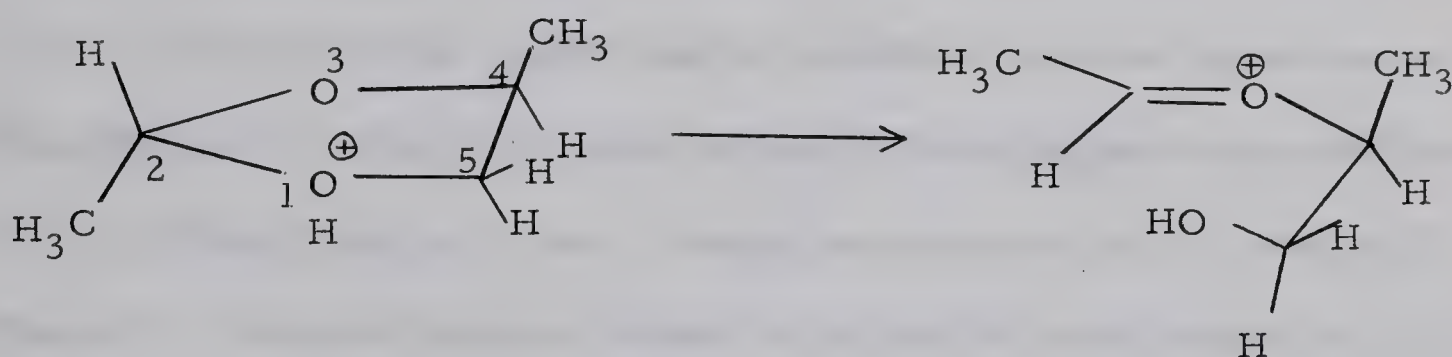


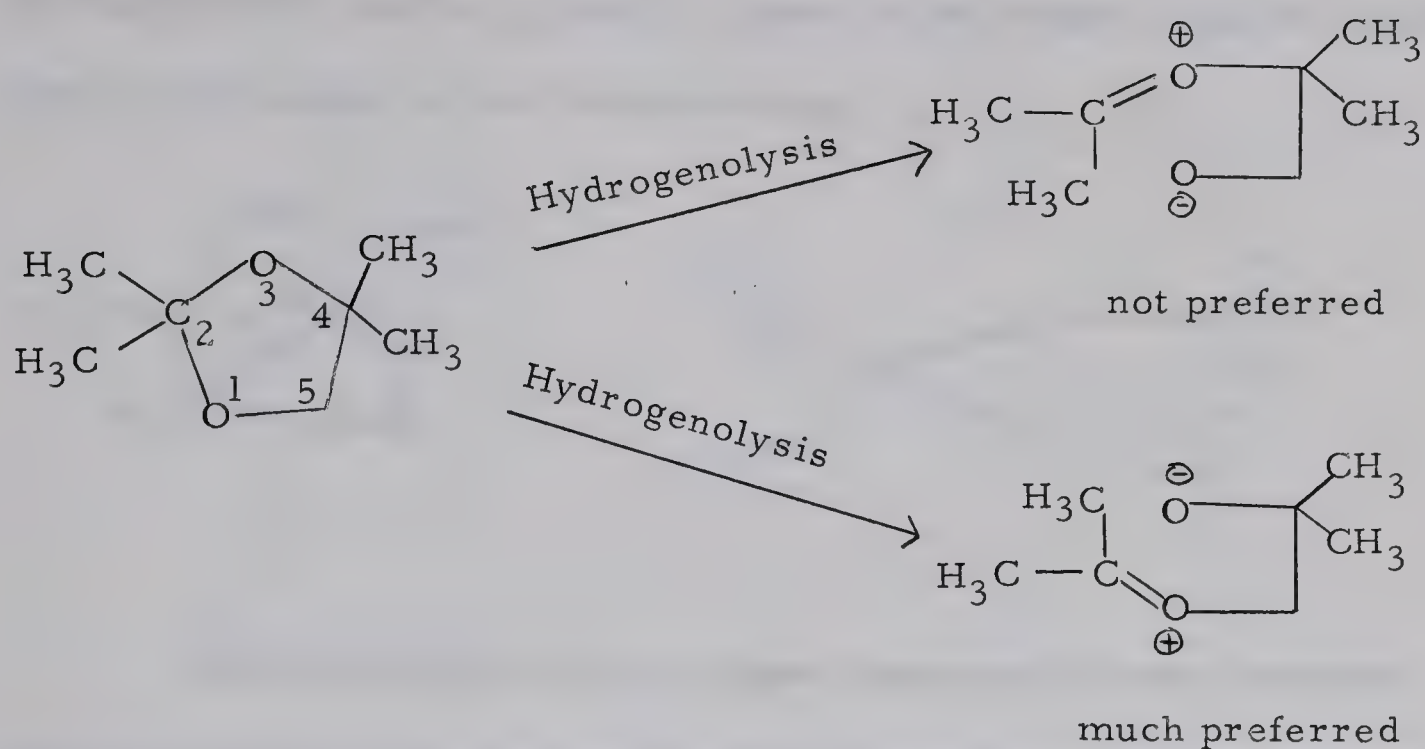
Chart 40b

(2) The observation that cis-2,4-dimethyl-1,3-dioxolane hydrolyzes about 4 times faster than does the trans isomer (Table IV, items 15, 16) was explained by Salomaa in similar terms. According to his view, when the carbonium ion is beginning to be formed, carbon 2 becomes sp^2 hybridized. The C_2 -methyl group, C_2 and its attached hydrogen atom become coplanar with O_3 and C_4 (see below). Salomaa postulated that in the case of the trans derivative, the methyl group at C_4 , being on the same side as the C_2 -H bond will retard the reaction, a situation not observed in the cis derivative:



A study of models leads us to believe here that there are no significant interactions between the methyl group at C_4 and the substituents at C_2 . Thus, we are inclined to believe that the above explanation is not satisfactory.

(3) If we look at the results of the hydrogenolysis of 2,2,4,4-tetramethyl-1,3-dioxolane found by Leggetter and Brown (44), we see that the direction of opening is the reverse of the one expected on the basis of polar effects. If steric effects were fundamental, it is difficult to explain how the Lewis acid ($AlClH_2$) coordinates preferentially with the oxygen 3 rather than with C_1 .



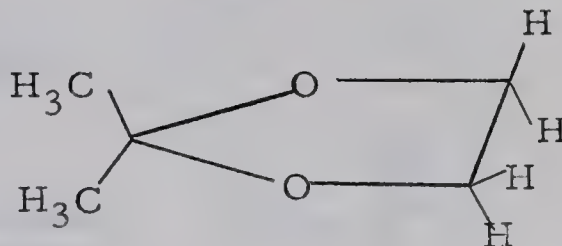
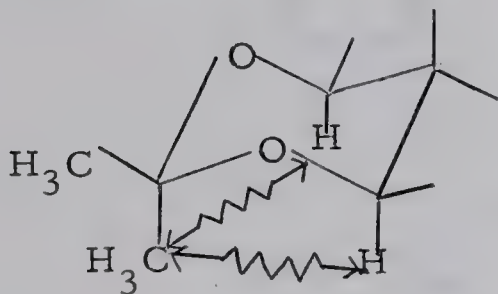
Whether these results can be explained in terms of entropies of activation or if there are other factors involved is yet to be clarified.

Steric effects, if any, change the rate by a factor of about 10^1 (Table IV, compare entries 15 and 16, 16 and 17, and 12 and 17). If we compare for example the 2,4,4,5,5-pentamethyl-1,3-dioxolane with the 2-methyl-1,3-dioxolane the difference is only a factor of 7. But these two differ themselves from the C_2 unsubstituted 1,3-dioxolane by factors of $10^{3.6}$ and 10^3 respectively.

It is interesting to note that the 2,2-dimethyl-1,3-dioxane hydrolyzes 30 times faster than does the 2,2-dimethyl-1,3-dioxolane, while each of them is respectively 6,800,000 times and 54,000 times faster than the unsubstituted parent compound. This difference, by a factor of 30, in reactivity could be explained perhaps in terms of strain from two 1,3-diaxial interactions, C//H, between the C_2 methyl group and the two

hydrogen atoms on the C_4 and C_6 , found in the dioxane ring (see below).

This is not present in the dioxolane ring.



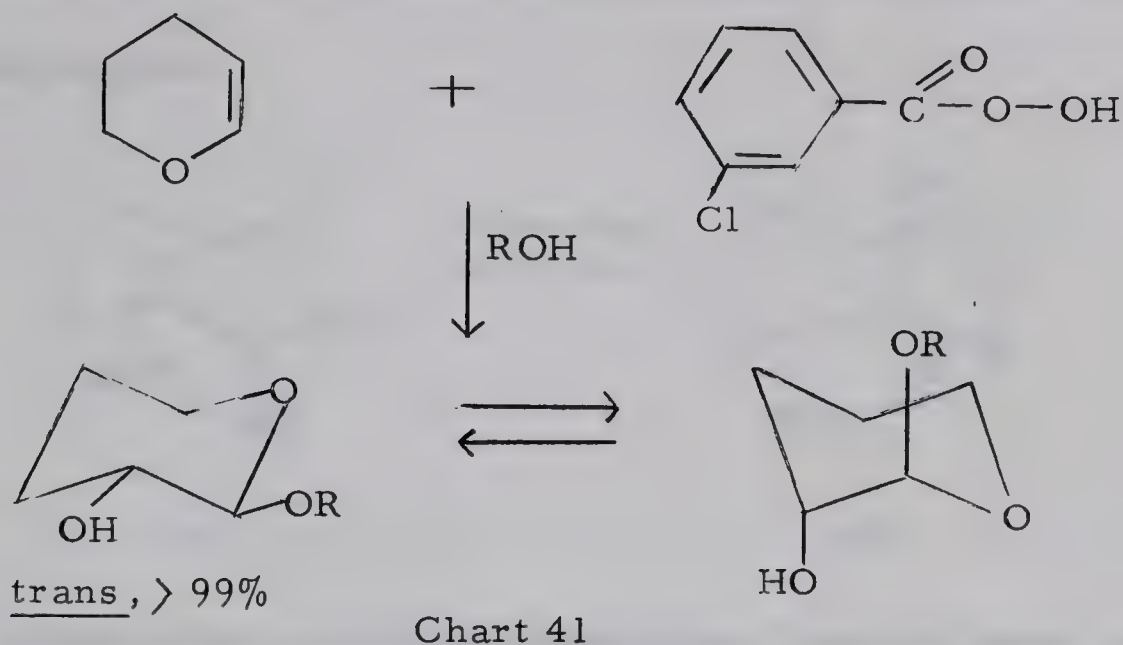
During hydrogenolysis of these compounds it was observed that the dioxane derivative was similarly more reactive than were the dioxolanes.

IX. Hydrogenolysis, by the Mixed Reagent, of trans 2-Alkoxy-3-Methoxytetrahydropyrans.

A number of 2-alkoxy-3-methoxytetrahydropyrans were subjected to hydrogenolysis to determine the influence of the 3-methoxy group on the rate and direction of C-O bond cleavage. Included also was an examination of the hydrogenolysis of the 6-methyl derivative of one of the above compounds.

The 3-methoxytetrahydropyrans were prepared according to Sweet and Brown (39) by reaction of m-chloroperoxybenzoic acid with 4,5-dihydropyran in the presence of the appropriate alcohol. In these reactions the trans compound was obtained nearly exclusively ($>99\%$), contaminated with only a trace of the cis isomer ($<1\%$) (Chart 41). The hydroxy compounds were methylated by the sodium hydride-methyl iodide

process (40).

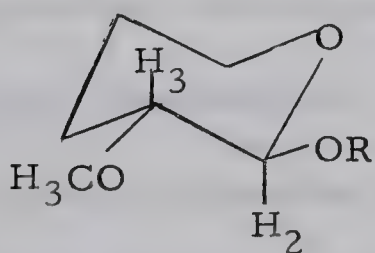


The cis compound did accumulate slowly under the influence of the acid present if one left the reaction mixture for some time before work-up.

Table VI shows some of the n.m.r. data for three of these compounds (53).

TABLE VI

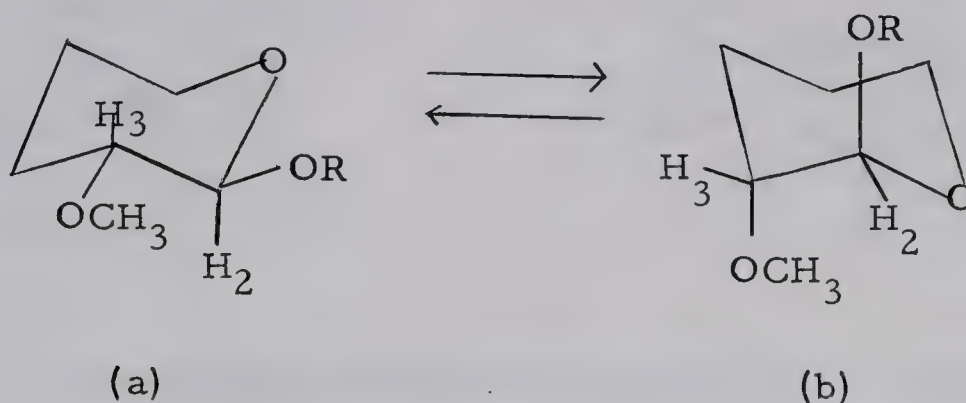
N.m.r. Data for Some trans-2-Alkoxy-3-methoxytetrahydropyrans.*



Substituent, R	Chemical Shift, τ_{C_2H}	Coupling Constant, $J_{2,3}$, c.p.s.
CH ₃	5.62	3.6
C ₂ H ₅	5.58	3.5
HC(CH ₃) ₂	5.34	4.0

* Taken from the work of Sweet and Brown (53).

Each of these compounds can be written in the following alternate chair conformations.



To determine the relative population of each of these conformers, the following formula (54) was employed.

$$J_{\text{obs}} = J_{\text{aa}} X_{\text{aa}} + (1 - X_{\text{aa}}) J_{\text{ee}}$$

where X_{aa} = Mole fraction of the conformer with H_2 and H_3 trans-diaxial;

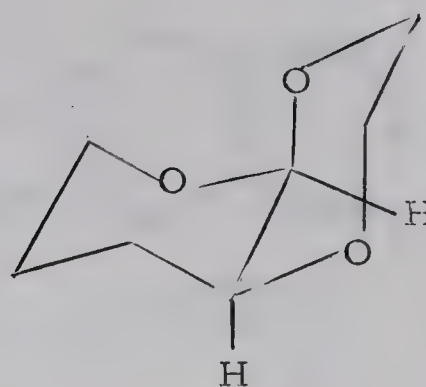
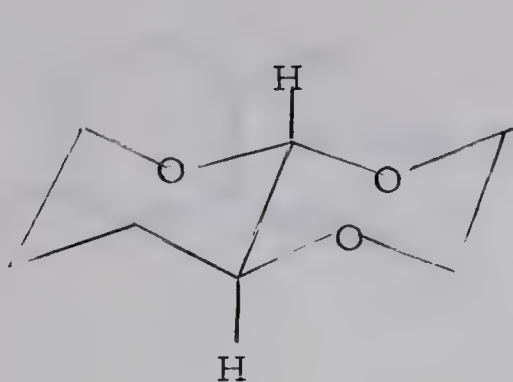
$1 - X_{\text{aa}}$ = Mole fraction of the conformer with H_2 and H_3 trans-diequatorial;

J_{aa} = Coupling constant corresponding to the conformer with H_2 and H_3 trans-diaxial;

J_{ee} = Coupling constant corresponding to the conformer with H_2 and H_3 trans-diequatorial;

J_{obs} = coupling constant observed experimentally.

Since the coupling constants $J_{\text{H}_2\text{H}_3}$ for the discrete conforms (a) and (b) are unknown, values were obtained from the bicyclic compounds recently prepared by Sweet and Brown (55). They are considered to be the best models yet available to obtain values for the spin-spin coupling, for 2-alkoxy-3-alkoxy(or hydroxy)tetrahydropyrans, of vicinal protons which have a dihedral angle of 180° (trans-diaxial) or 60° (trans-diequatorial).

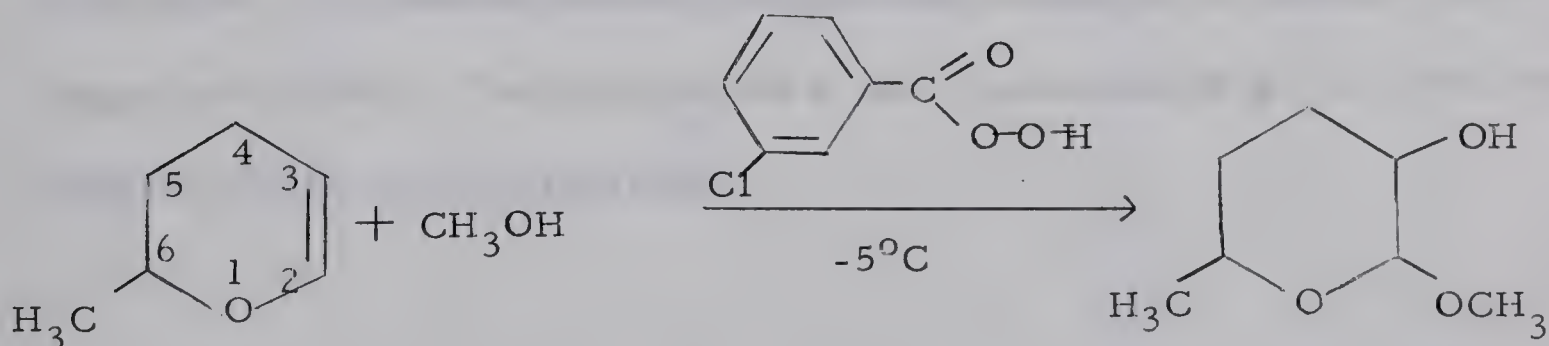


cis- and trans-tetrahydropyrano(2,3-b)-1,4-dioxane

These couplings were found to be 7.1 c.p.s. and 1.3 c.p.s. respectively.

By calculation, the proportion of conformer (a) to conformer (b) was found to be 40 to 60% in the case of the 2,3-dimethoxy- and 2-ethoxy-3-methoxytetrahydropyran. This proportion increased to 47% for the conformer (a) in the case of the 2-isopropoxytetrahydropyran.

To determine the influence of an electron donating group at C₆ in the 2,3-dialkoxytetrahydropyrans, 6-methyl-2,3-dimethoxytetrahydropyran was prepared, following the same procedure used for the 2,3-dialkoxy derivatives (Chart 42).



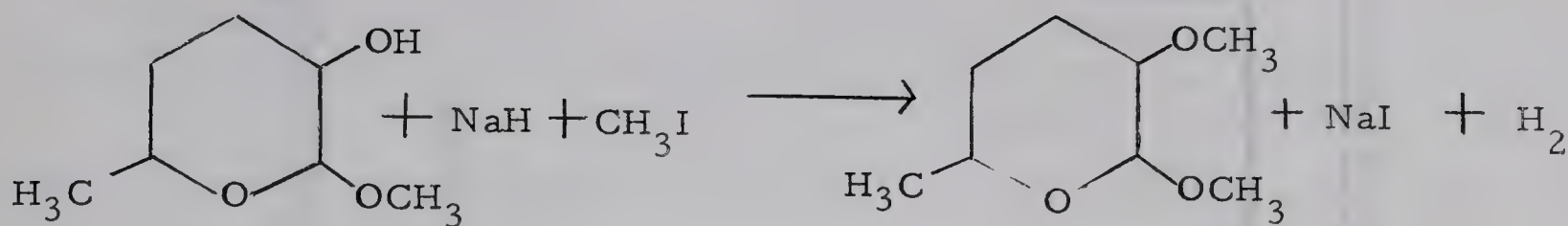


Chart 42

As shown by Sweet and Brown (39) this method of peroxydation gives predominantly the C₂-C₃ trans product. Accordingly the conformations of this trans product are those below in (Chart 43).

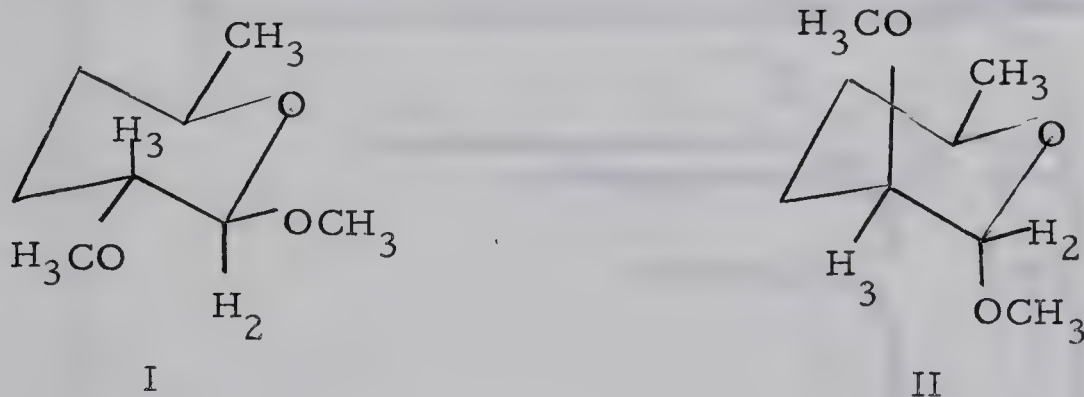
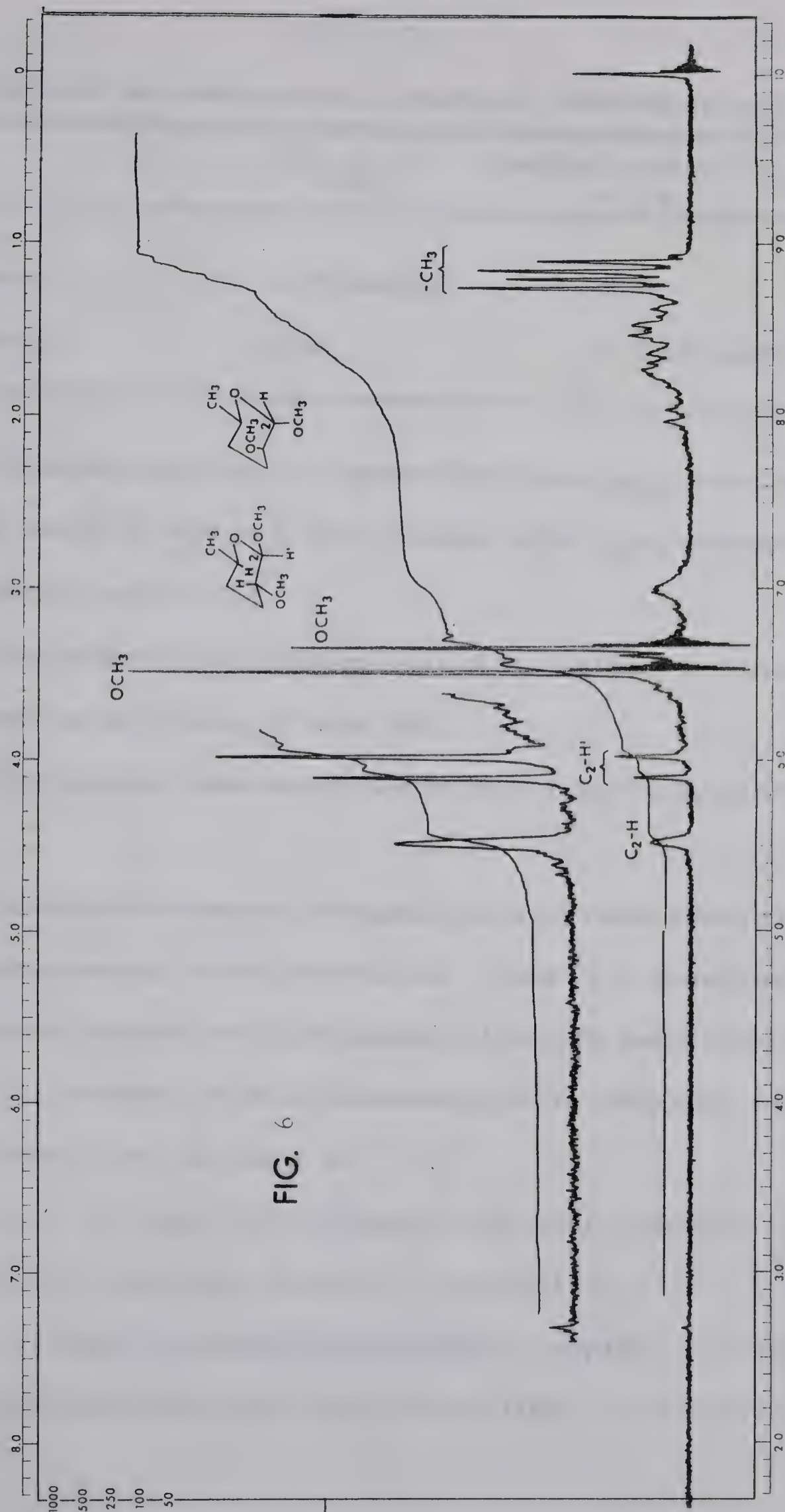


Chart 43

The C₆ methyl group was reasonably assigned the equatorial orientation, for reasons already exhaustively explained in similar cases (pages 49 to 54). The data for the n.m.r. spectrum (Fig. 6) of the two isomers can be seen in Table VII.



N. m. r. spectrum of the cis,trans 6-methyl-2,3-dimethoxytetrahydropyran.

TABLE VII

N.m.r. Data for the Isomers of the 6-Methyl-2,3-dimethoxytetrahydropyran.

	$\tau, \text{C}_2\text{H}$	Coupling constant, $J_{2,3}$, c.p.s.
Isomer I	5.95 (doublet)	7.5
Isomer II	5.52	3 (half width)

These data seem to be in agreement with a trans-diaxial arrangement of H_2 and H_3 in isomer I, and similarly with a trans-diequatorial arrangement for isomer II.

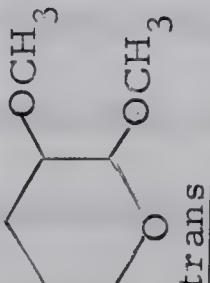
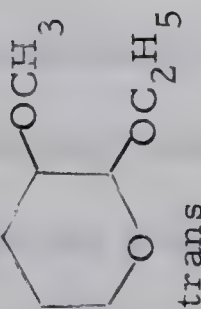
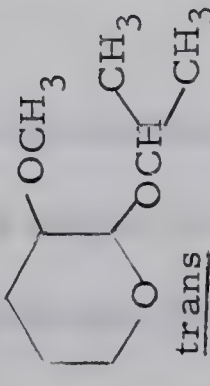
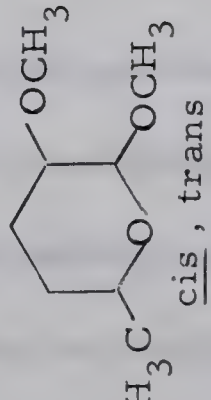
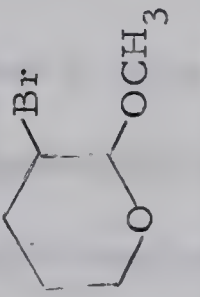
The results of the hydrogenolysis of the 2-alkoxy-3-methoxy-tetrahydropyrans are shown in Table VIII.

The following observations can be made from the data in Table VIII.

- 1) The 3-methoxy derivatives hydrogenolyze much more slowly than do the corresponding 3-deoxy derivatives. Thus, 2,3-dimethoxytetrahydropyran was reduced to the extent of 15% in 96 hours (Table VIII, entry 1), whereas 2-methoxytetrahydropyran is completely reduced in 16 hours (Table IIa, expt. 1).
- 2) The rate of hydrogenolysis increases in the order 2-methoxy < 2-ethoxy \approx 2-isopropoxy (Table VIII, entries 1-3).
- 3) Of the 2-alkoxy-3-methoxytetrahydropyrans, only the 2-methoxy derivative gives some side chain cleavage (40%). The others react

TABLE VIII

Hydrogenolysis of Some 2-Alkoxy-3-methoxytetrahydropyrans

Compound	Expt. No.	Reduction time, hrs.	Extent of Reduction, %	Recovery, %	Side Chain Cleavage, %	Ring Cleavage, %
 <u>trans</u>	1	5 18 96	0 0 15	85 75 80	- - 40	- - 60
 <u>trans</u>	2	5 5	22 25	90 88	0 0	100 100
 <u>trans</u>	3	5	22	80	0	100
 <u>cis, trans</u>	4	5 22	0 12	>80 82	100	0
 <u>cis and trans</u>	5	24 48	0 0	>80 >80	- -	- -

*This compound has been included here to show the effect of an electron withdrawing group other than $-\text{OCH}_3$ and $-\text{OH}$ in position 3.

via ring cleavage only (Table VIII, entries 1-3). The introduction of a methyl group at C₆ changes the picture completely since the only product observed was that of side chain cleavage. In this case, the C₆-CH₃ group increased the rate of hydrogenolysis over that found for the parent compound (Table VIII, cf. entries 1 and 4), but this increase did not approach that observed when the C₂-alkoxy group was changed from -OCH₃ to -OC₂H₅ or -OC₃H₇ (Table VIII, entries 1-3).

4) There is a smaller proportion of side chain cleavage to ring cleavage obtained from the 1,2-dimethoxytetrahydropyran than was found for the 2-methoxytetrahydropyran (70% side chain cleavage for the latter, Table IIa, expt. 1; 40% side chain cleavage for the former). Thus it is likely that the rate of reduction is different when reaction occurs via side chain cleavage as compared with ring cleavage and according to the above results ring cleavage appears to be the faster process in the C₃-methoxy substituted tetrahydropyranyl ethers. However this point requires further study.

It is obvious that a substituent at C₃ not only has a marked effect in the rate of hydrogenolysis (as expected) but also has a bearing on the direction of cleavage.

During the discussion of the different proportions of side chain cleavage versus ring cleavage with respect to the hydrogenolysis of the 2-alkoxytetrahydropyrans we showed that it is unlikely that steric effects, hindering the approach of the Lewis acid to the ring oxygen or side chain

oxygen, are of primary importance in this process. We assume that this prevails in the present situation.

We might expect a large difference in the rate of hydrogenolysis between the various C_2 -alkoxy compounds if the intermediate carbonium ion were of the type I (Chart 44) since the stability of this ion is affected by the substituent R on the exo oxygen.

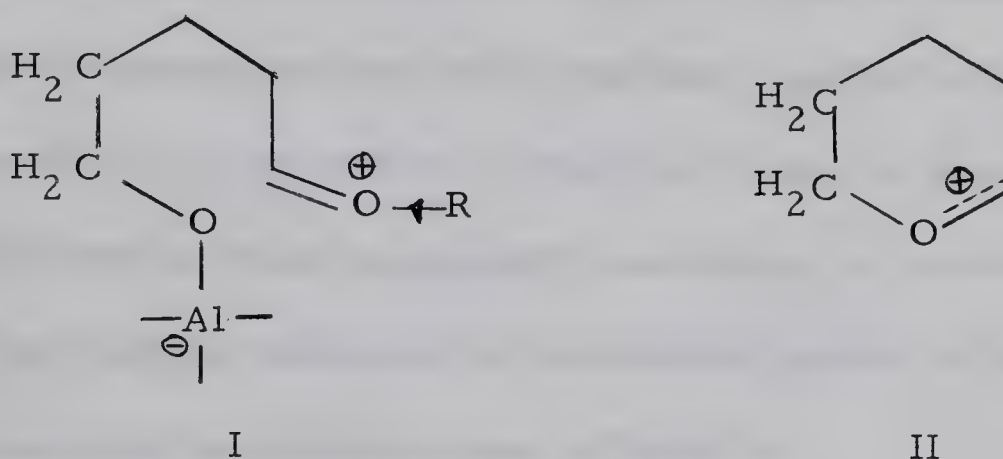


Chart 44

This is in line with the experimental results. One would expect no appreciable difference in rate, between the 2-methoxy and 2-ethoxy and isopropoxy compounds, if the intermediate carbonium ion were of the type II (Chart 44). In the case of the 2,3-dimethoxytetrahydropyran, intermediate I is preferred over intermediate II according to the proportion 60% to 40% (Table VIII, entry 1 shows 60% ring cleavage). This preference increases to 100% when the R group is ethyl or isopropyl.

A rationalization with regard to the facts discussed above can be offered in the light of recent published information. Certain analogies with the situation described here have appeared in the literature. The

possibility has been mentioned of nucleophilic assistance to hydrolysis of glycosidic bonds catalyzed by enzymes (56). However no proof was available to substantiate this view. Recently, Capon and Thacker (57) reported evidence of nucleophilic assistance in the rupture of the glycosidic bond. Since it is well known that the acid-catalyzed hydrolysis of acetals and glycosides proceeds according to an A-1 mechanism (see page 31) without nucleophilic participation of the molecules of water (42), Capon and Thacker decided that any acid-catalyzed reaction of acetals or glycosides that proceeds by a route different from A-1 could be considered as support of an hydrolysis in which nucleophilic assistance is involved. Consequently, they carried out the hydrolysis of the dimethyl acetal of D-glucose and of D-galactose with the results shown in Table IX.

TABLE IX

Hydrolysis of the Dimethyl Acetal of D-Glucose and D-Galactose in Acid

Medium at 35°C.*

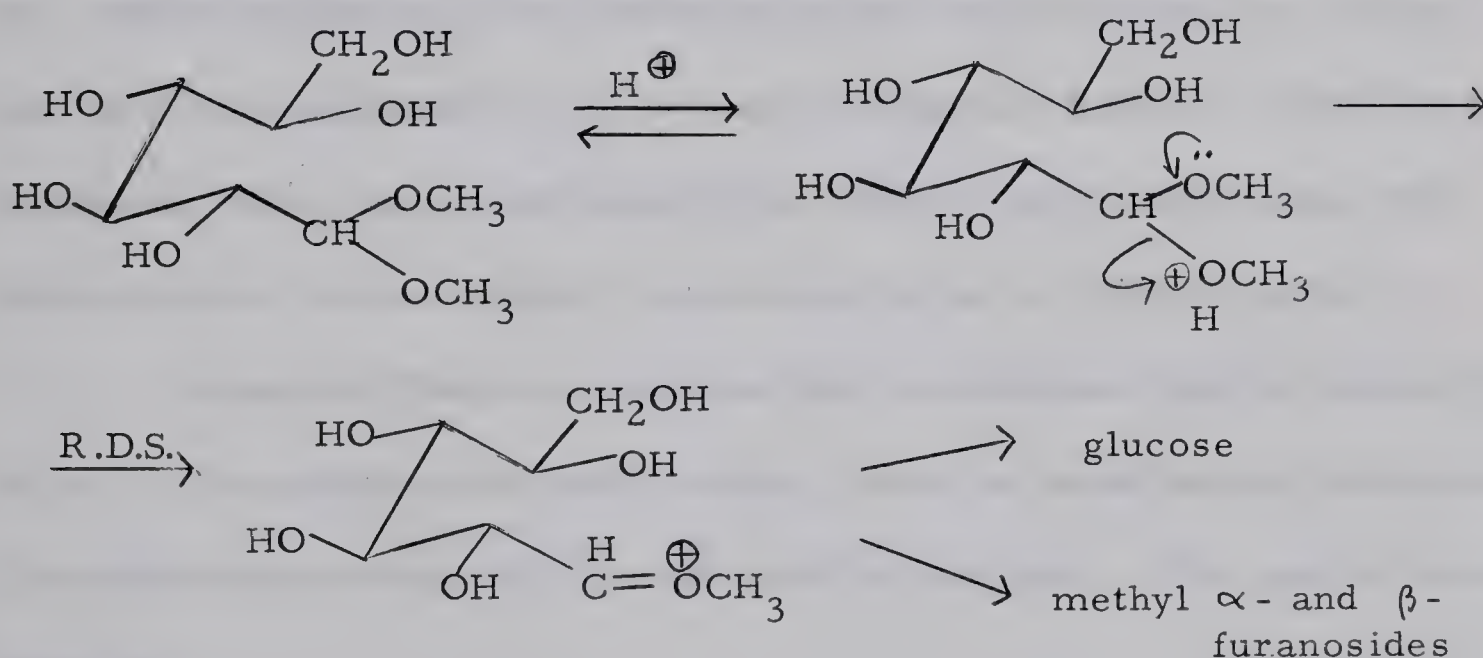
Dimethyl acetal of	Concentration of HCl (molar)	Kinetically controlled products, % yield			$10^4 k$ sec ⁻¹
		Aldose	Furanosides	Pyranosides	
D-glucose	0.05	<2	>98	<0.5	17
D-galactose	0.05	29	71	0.5	1.58

* Taken from the work of Capon and Thacker (57).

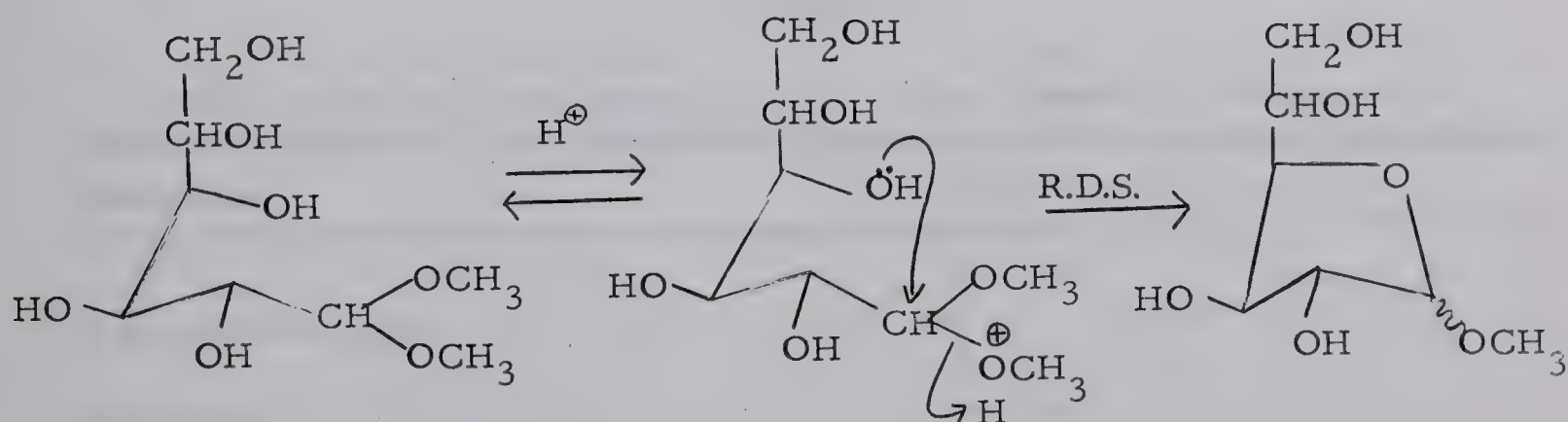
Under these conditions the dimethyl acetals gave not only the expected aldose, resulting from hydrolysis, but also a high proportion of the α - and β -furanosides, which arose from ring closure. Pyranosides were also obtained, but in very small amounts.

The following two mechanisms were considered possible for the ring closure to furanosides. The example employed is the dimethyl acetal of D-glucose.

Mechanism I



Mechanism II



According to mechanism I, the total rate \underline{k} should be independent of the configuration about C_4 . By mechanism II, the rate of ring closure, that is to say, the total rate \underline{k} , depends on the configuration about C_4 . The fact that the D-glucose dimethyl acetal reacts 10 times faster than does the D-galactose dimethyl acetal, and that the proportion of furanoside is higher for the D-glucose dimethyl acetal is good support, according to the authors, for mechanism II. It should be noted that in the first mechanism the rate determining step is given by what the authors call the "rate of ionization", the formation of the oxocarbonium ion, of the type found in the hydrolysis of ordinary acetals and ketals. In the second mechanism the rate is controlled by the ring closure synchronous with the rupture of the acetal bond, to produce the α or β -furanoside.

Capon and Thacker compared the rate obtained for the hydrolysis of the D-glyceraldehyde dimethyl acetal, with the rates for the hydrolysis of the dimethyl acetals of D-glucose and D-galactose. This can be seen in Table X.

TABLE X

Acid-catalyzed Hydrolysis at 25°C of the Dimethyl Acetals of *

Compound	$10^4 k, 1 \text{ mole}^{-1} \text{ sec}^{-1}$
D-glyceraldehyde	1.77
D-glucose	110
D-galactose	9.3

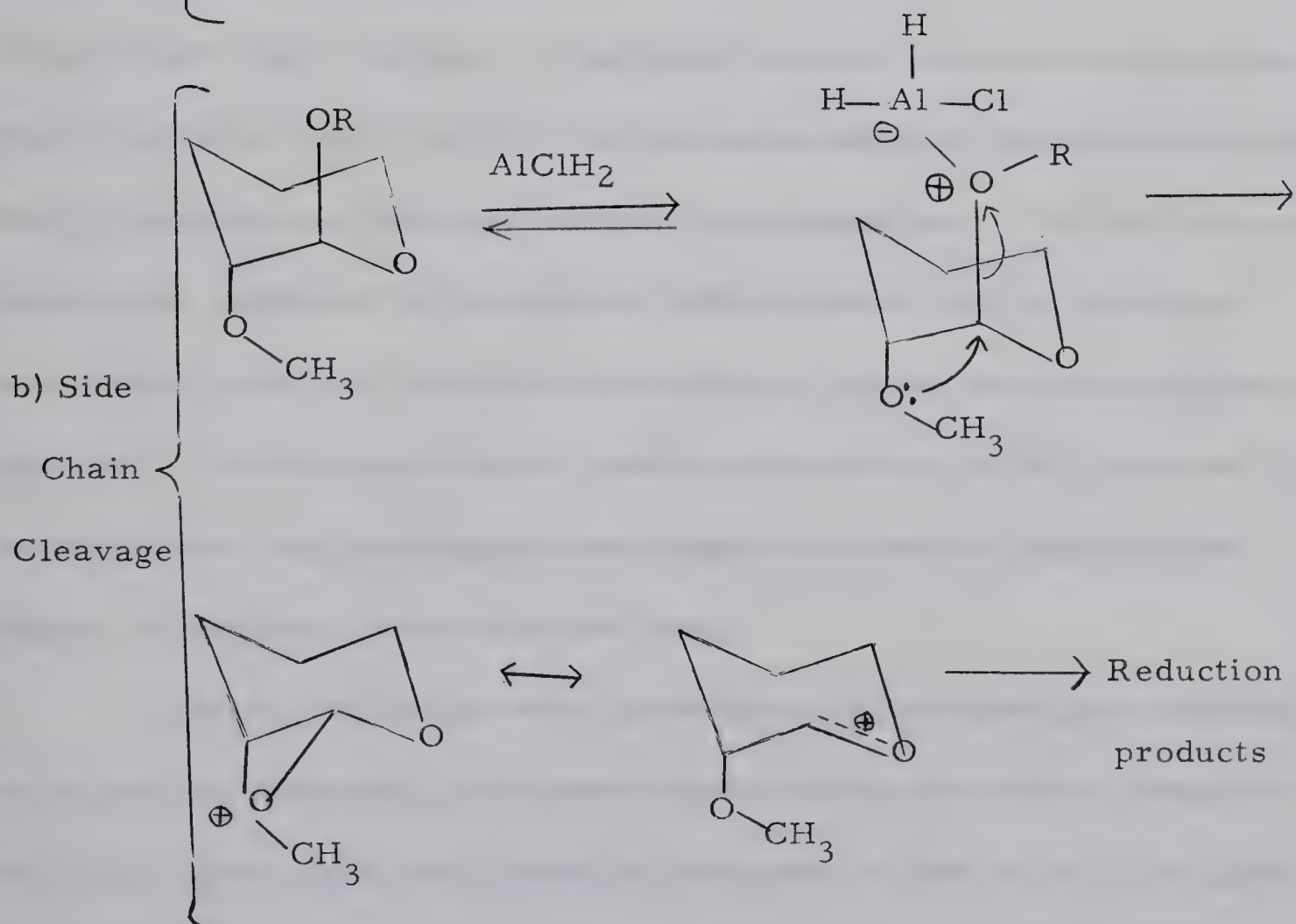
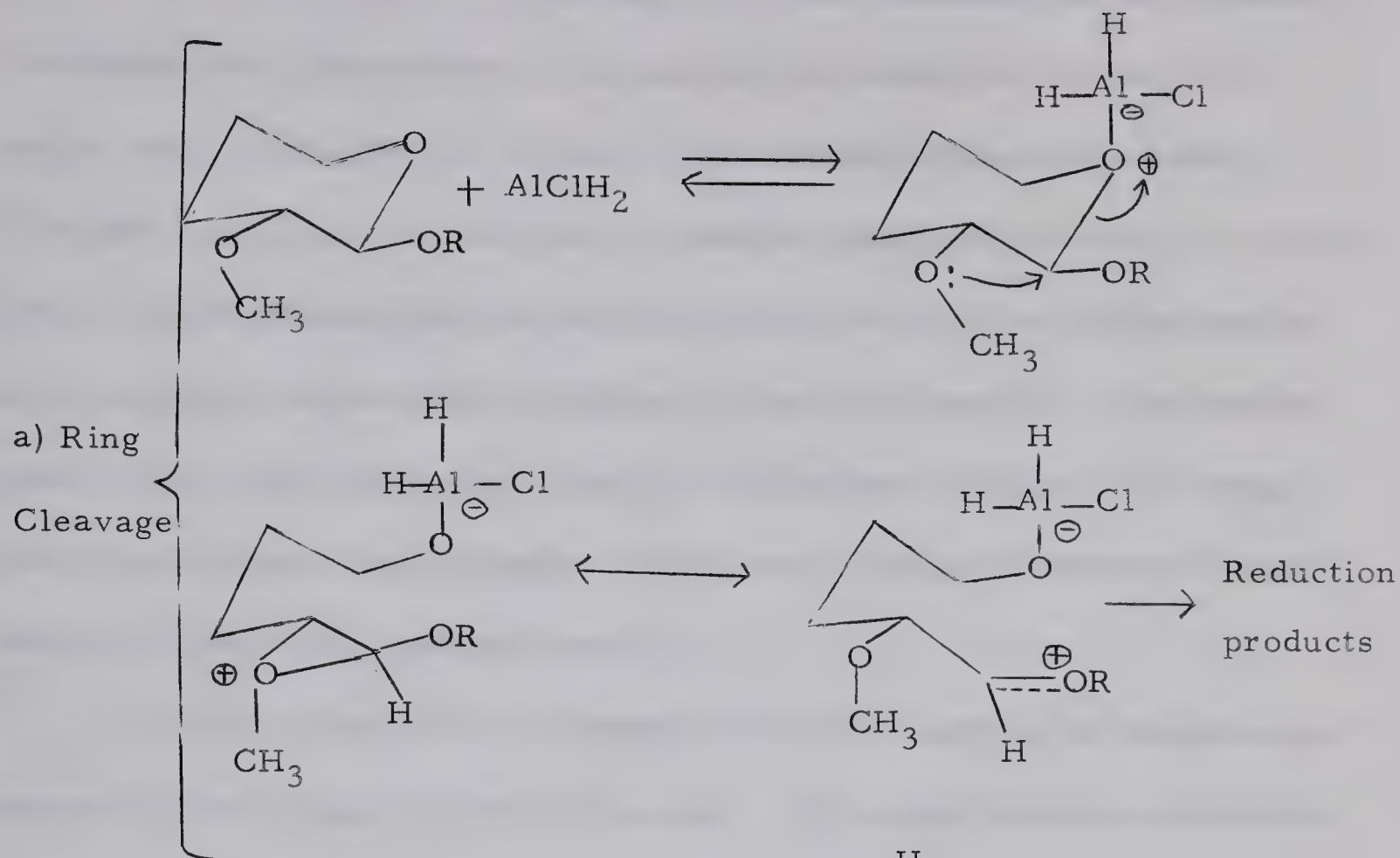
*Taken from the work of Capon and Thacker (57).

For the D-glyceraldehyde dimethyl acetal, the rate observed is considered to represent the rate of ionization. Since the rates for the two sugar acetals studied are considerably larger than is the rate for the D-glyceraldehyde acetal, the authors concluded that the fact of anchimeric assistance and synchronous rupture of the acetal bond is well established.

The possibility exists then of a similar participation, via nucleophilic assistance of a properly situated substituent, in the hydrogenolysis of the 2,3-dialkoxytetrapyrans.

Recalling what was said on page 84 concerning the conformation of these molecules, it is clear that in the ground state they exist in two conformations in nearly equimolar proportions. Upon hydrogenolysis, there are two possible intermediate carbonium ions that can be formed (Chart 44, I and II, page 90). Considering only the influence of the R group, carbonium ion II should be preferred only in the case of the 2,3-dimethoxytetrahydropyran (the electron donating power of an "ethyl" group is larger than that of a methyl group).

Now, if we consider participation of the methoxy group at C₃ we have the following situation for the two conformers in which the favoured route for C-O bond breaking is that which involves structures having the optimal trans arrangement of the relevant groups.



Considering the hydrogenolysis results obtained for the 2-ethoxy-3-methoxy and 2-isopropoxy-3-methoxytetrahydropyrans (Table VIII, page 88), oxocarbonium I (page 90) is favored in these two cases. This fact, considered in the light of possible participation of the C₃-methoxy group, would indicate that the molecule reacts with its two alkoxy groups at C₃ initially diequatorial as depicted in the first case (a). The methoxy group at C₃ is located trans to the C₂-ring oxygen, the physical arrangement which favors ring cleavage. Only ring cleavage is observed experimentally (Table VIII, entries 2 and 3).

In the case of the 2,3-dimethoxytetrahydropyran we should expect oxocarbonium II (page 90) to be favored. We should therefore anticipate largely side chain cleavage, if the stabilization of the oxocarbonium ion due to the polar nature of the alkyl groups attached to the ring oxygen or the exo oxygen were the only factor to be considered. The fact that ring cleavage is produced to the extent of 60% indicates that the reacting conformer is the one in which the two alkoxy groups are in the diequatorial position. In this conformation, participation of the -OCH₃ group at C₃ to bring about ring cleavage becomes operative and this explains the higher proportion of oxocarbonium ion I.

However, since as much as 40% side chain cleavage was actually produced, neighbouring group participation does not overrule completely the polar effect of the ethyl group as compared to that of the -CH₃ group (see carbonium ion II, Chart 44, page 90).

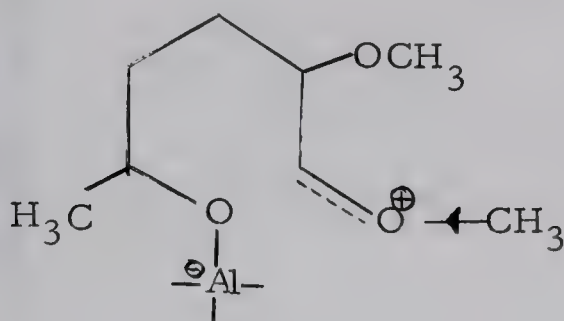
The difference in reactivity of the 2,3-dimethoxytetrahydropyran as compared with the 2-ethoxy- and 2-isopropoxy homologues can be explained in terms of the ratio of the oxocarbenium ions formed (I and II, Chart 44).

Due to the participation of the $-OCH_3$ group at C_3 , carbonium ion I is formed to the extent of 60%, in the case of the 2,3-dimethoxytetrahydropyran. This is not the most favored ion in the case of this particular molecule in terms of polar effects. On the other hand, for the 2-ethoxy and 2-isopropoxy homologues, ion I is the most favored one, and this is the one formed (100%) due to the above mentioned participation of the $-OCH_3$ group.

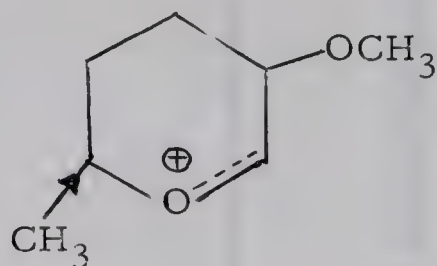
As a final point, it is important to notice that the oxygen of the C_3OCH_3 group by its anchimeric assistance does not stabilize the positive charge on C_2 as effectively as do the resonance and polar effects of the exo or ring oxygens, with their respective attached alkyl groups. But the inductive effect of this C_3 -methoxy group is always operative and strong with the result that all of the 3-methoxy derivatives hydrogenolyze much more slowly than do the corresponding 3-deoxytetrahydropyranyl ethers.

The influence of a methyl group at C_6 was shown by the hydrogenolysis of the 6-methyl-2,3-dimethoxytetrahydropyran. The isomeric mixture of this compound gave exclusively the product arising from side chain cleavage. It is clear that because of the C_6 -methyl group the

intermediate carbonium ion III is much less stable than is ion IV and that other effects are less important. The experimental result certainly agrees with the result expected from an electron releasing group at C₆.



III



IV

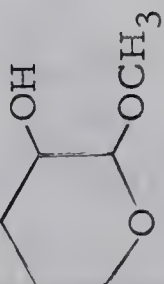
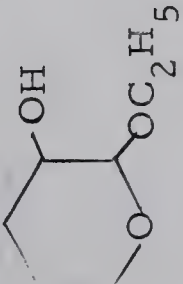
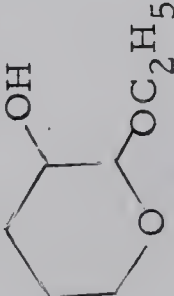
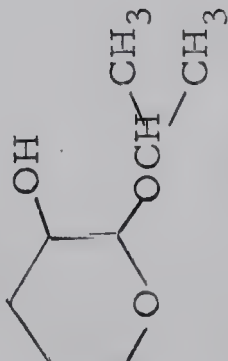
X. Mixed Reagent Hydrogenolysis of trans-2-Alkoxy-3-hydroxytetra- hydropyrans.

We saw that the introduction of a methoxy group at C₃ resulted in a substantial decrease in the rate of hydrogenolysis and also in a change in the amount of ring cleavage of the tetrahydropyranyl ethers compared to that which was found for the C₃-unsubstituted 2-alkoxytetrahydropyrans.

Hydrogenolysis of the 2-alkoxy-3-hydroxytetrahydropyrans (Table XI) shows that the hydroxyl group at C₃ also retards the hydrogenolysis but less so than does the C₃-OCH₃ group. Furthermore, the hydroxyl group at C₃ also influences the direction of cleavage, analogous to the changes caused by the C₃ methoxy group. However in all cases only ring cleavage was observed. Using the n.m.r. data for the 3-hydroxytetrahydropyranyl ethers (55), assembled in Table XII, along with the formula $J_{\text{obs}} = J_{\text{aa}}X_{\text{aa}} + J_{\text{ee}}(1 - X_{\text{aa}})$ (page 83) we find that the ratio of the conformer having the HO- and -OR groups diequatorial, to the

TABLE XI

Hydrogenolysis of Some trans-2-Alkoxy-3-hydroxytetrahydropyrans

Compound	Expt. No.	Reduction time, hrs.	Extent of Reduction, %	Total Recovery, %	Side Chain Cleavage, %	Ring Cleavage, %
	1	3	0	80	-	-
	2	5	0	85	-	-
	3	96	15	83	-	100
	4	4	61	85	-	100
	5	17	100	80	-	100
	6*	4	62	80	-	100
	7	5	100	85	-	100
	8	17	100	80	-	100

*Reduction done using the procedure of adding the acetal to the previously prepared species (AlClH_2).

conformer with these groups diaxial (Chart 45) is 69%:31%, for the 2-methoxy-3-hydroxytetrahydropyran and 72%:28% for both 2-ethoxy- and 2-isopropoxy- homologues. In this respect there is a marked difference

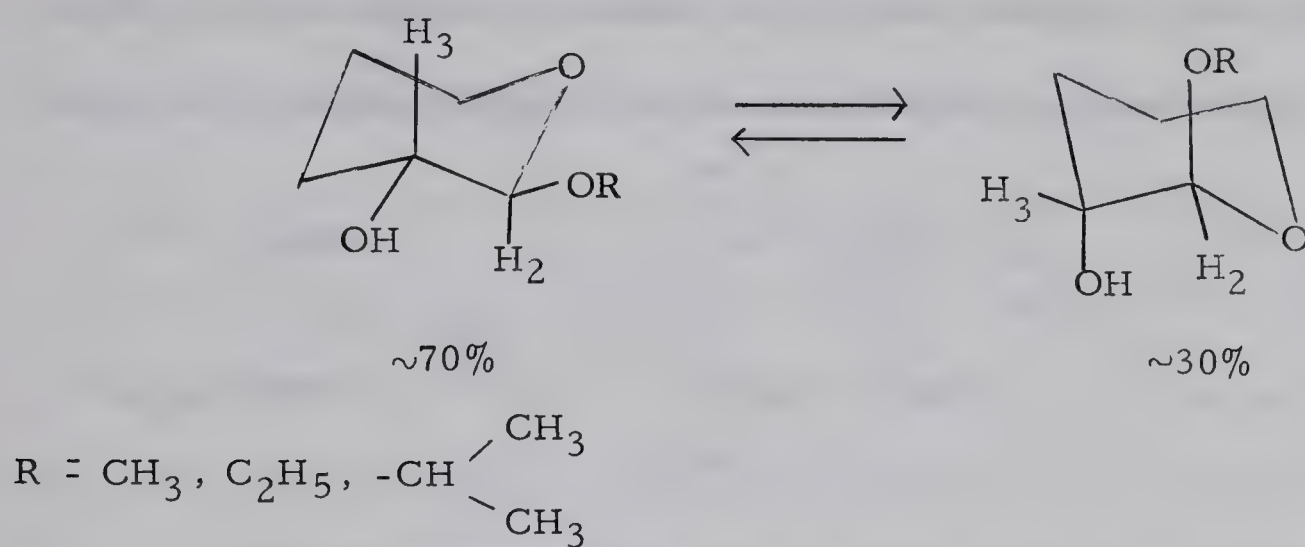


Chart 45

TABLE XII

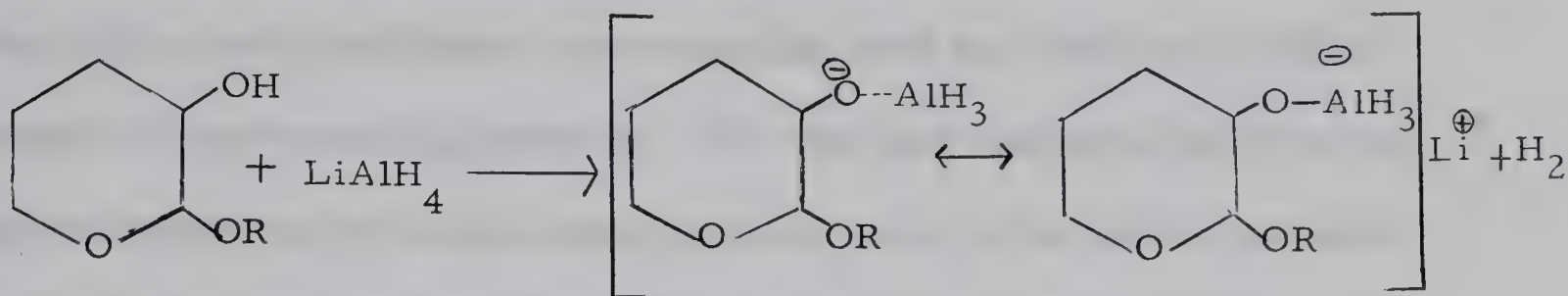
N.m.r. Data for Some 2-Alkoxy-3-hydroxytetrahydropyrans. *

Compound	Resonance signal, for H_2 ,	Coupling Constant, $J_{\text{H}_2\text{H}_3}$, c.p.s.
	5.79	5.3
	5.72	5.5
	5.66	5.5

* Taken from the work by Sweet and Brown (55).

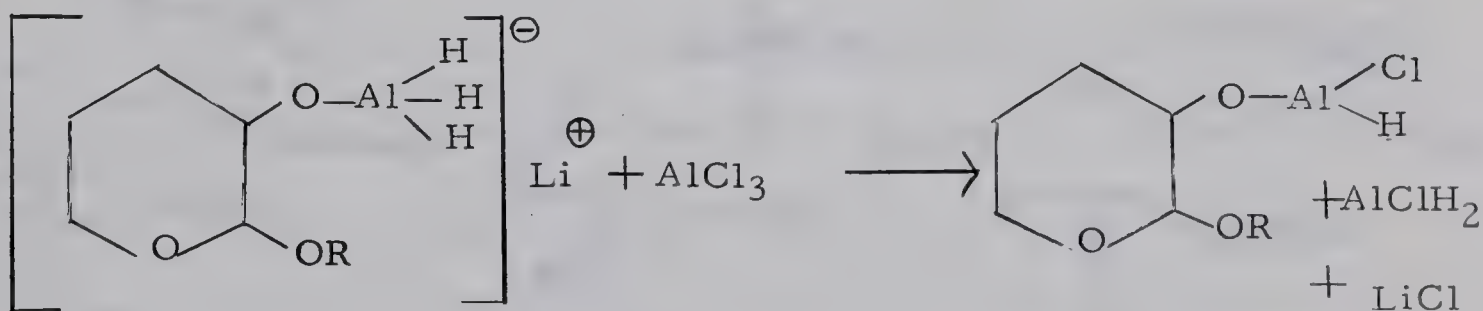
between the 2-alkoxy-3-hydroxytetrahydropyrans and the 2,3-dialkoxytetrahydropyrans.

It is quite likely that the -OH group reacts with the hydride when LiAlH_4 and the acetal are mixed (before the addition of the AlCl_3 , using Leggetter's method (1)) to form the alcoholate as shown below.

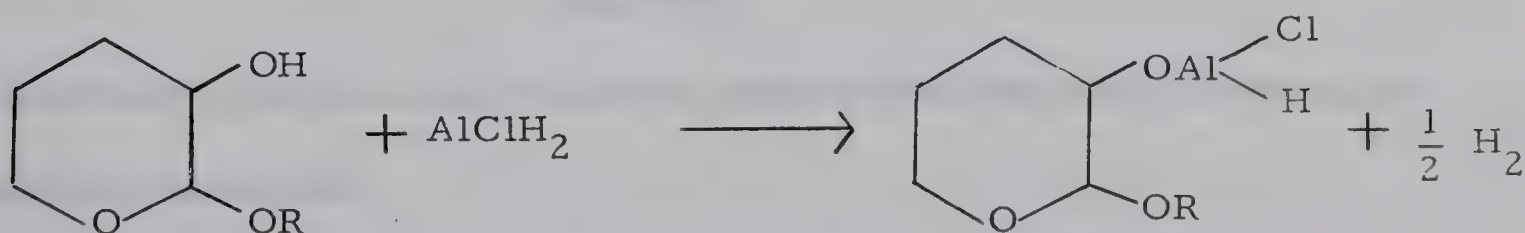


This is supported by the observation that a copious evolution of H_2 took place when the two substances were mixed together.

This alcoholate could react with the AlCl_3 by a reaction similar to that between LiAlH_4 and AlCl_3 shown by Ashby and Prather (32).



The same result would be obtained by the reaction between the species AlClH_2 and the 2-alkoxy-3-hydroxytetrahydropyran (Table XI, expt. 6).



This view is supported by the fact that the results of hydrogenolysis were the same for either method of reduction, whether we added the acetal to the $\text{LiAlH}_4/\text{AlCl}_3$ mixture or whether we added the AlCl_3 to the mixture of LiAlH_4 /acetal (Table XI, cf. expts. 4 and 6).

Due to the bulkiness of the $-\text{OAlClH}$ group it is quite likely that the molecule will react preferentially with the $-\text{OR}$ and $-\text{OAlClH}$ groups in the equatorial position. We also saw that originally (in the ground state) the molecule exists preferentially in the conformation in which the groups $-\text{OR}$ and $-\text{OH}$ are in the diequatorial positions. In such a structure the alumino oxy group is nicely arranged trans to the $\text{C}_1\text{-O}$ bond for anchimeric participation to form the intermediate carbonium ion by ring cleavage (Chart 46).

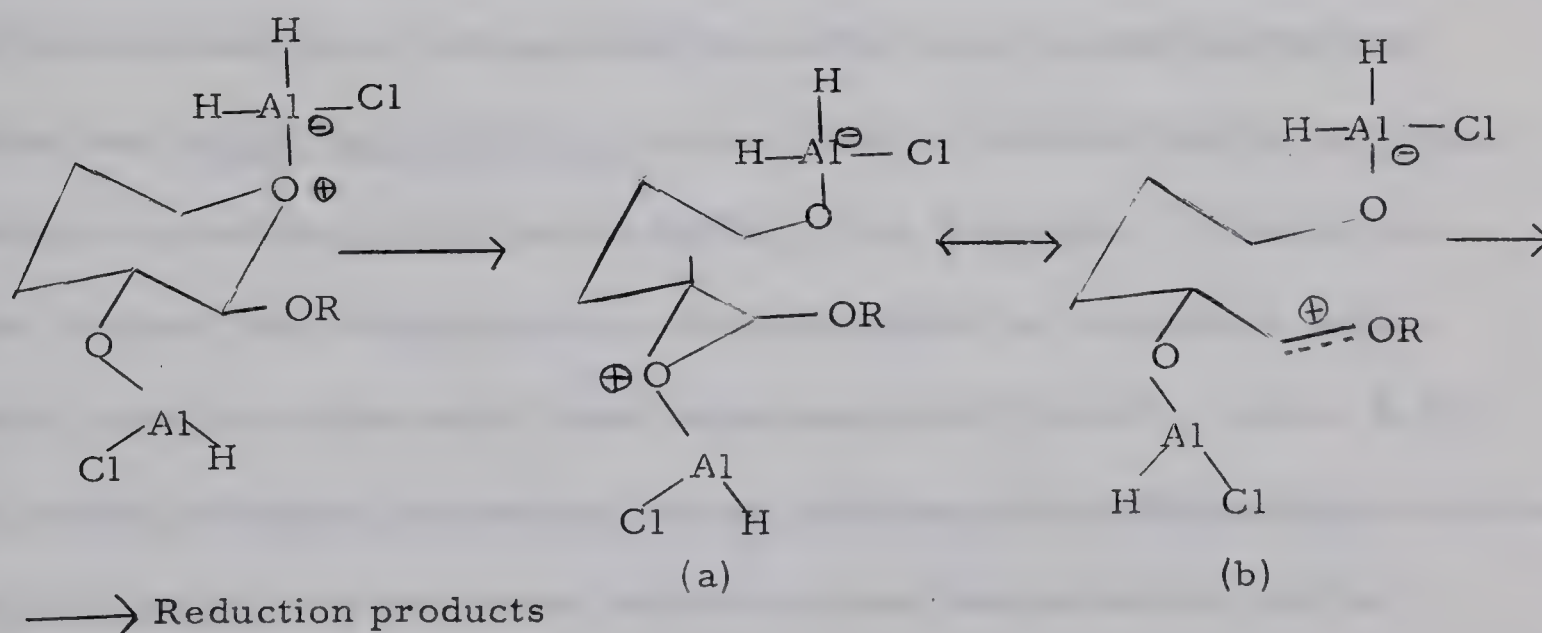


Chart 46

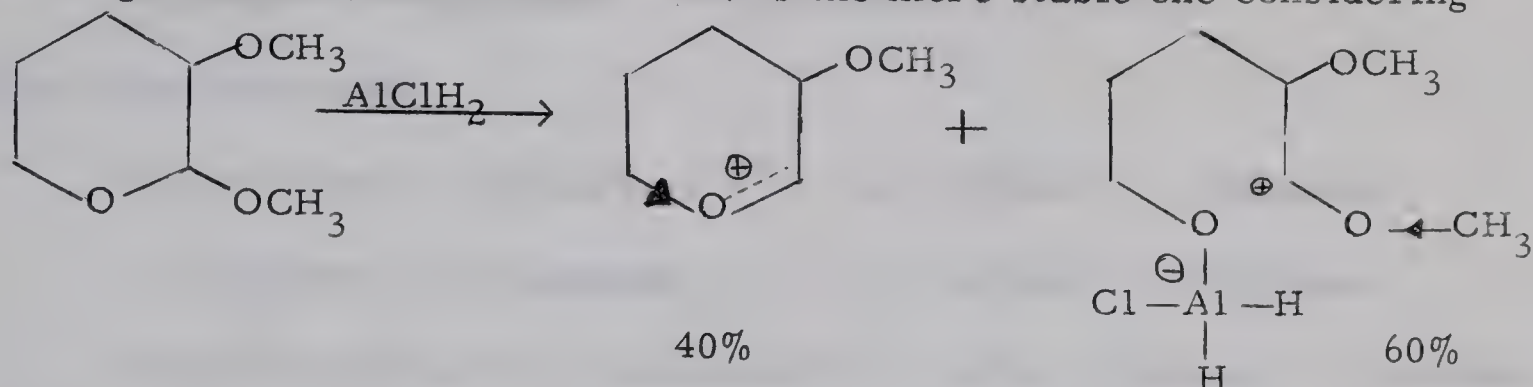
Accordingly ring cleavage should be greatly favored, and this is in fact the result obtained.

Also we observe that with the exception of the 2-methoxy

homologue, the 2-alkoxy-3-hydroxytetrahydropyrans are more reactive than are the corresponding 2-alkoxy-3-methoxytetrahydropyrans (cf. Table VIII and Table XI). The rationale behind the explanation of this fact takes into consideration the loss of the electron withdrawing effect when we replace the C_3-OCH_3 group by the $C_3-OAlClH$ group. In this latter case, the oxygen becomes negatively charged, and in this way destabilization of the oxocarbonium ion intermediate is greatly decreased.

For this oxocarbonium ion the resonance structures (a) and (b) (Chart 46) can be written. Since the reduction step is very likely a fast process, we postulate that the geometry of this carbonium ion won't be too much different from that of the original structure. By inspection of this carbonium ion and applying the same line of reasoning that have been used all through this thesis we see that its stability will be increased with increased electron donating ability of the R groups. If this is so, the 2-ethoxy and 3-isopropoxy derivatives should be the more reactive ones, and this is the result found experimentally (Table XI, expts. 4-8). A similar situation is observed for the 3-hydroxy-2-methoxytetrahydropyran. In this case the carbonium ion which is formed exclusively is not the one that, according to the inductive effects only, we would expect to be the more stable one. And experimentally this molecule is found to be the least reactive of the series. As a final point it is interesting to notice that the 2,3-dimethoxy and 3-hydroxy-2-methoxytetrahydropyrans

show practically the same extent of reactivity. Since the 2,3-dimethoxy-tetrahydropyran undergoes some degree of side chain cleavage (40%), this means that 40% of the intermediate carbonium ion formed is the one arising from ring retention, see below. This is the more stable one considering



the polar effects of the ethyl and methyl groups. On the other hand we saw that the 3-hydroxy-2-methoxy homologue undergoes 100% ring cleavage via the formation of the ion which in terms of polar effects should be the less stable. However, the 2,3-dimethoxytetrahydropyran is under the influence of the destabilizing effect of the $-OCH_3$ group at C_3 , an effect that has been greatly reduced in the case of the 3-hydroxy homologue, by reaction of the $-OH$ group with the $AlClH_2$.

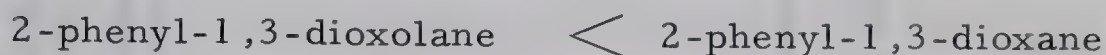
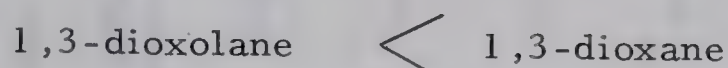
The effects presumably cancel out and the final result is the similar reactivity shown by the two compounds.

XI. Competitive Reductions of Mixtures of Dioxanes and Dioxolanes.

The findings of Ceder (25) and Leutner (21, 22) showed that 5-membered ring acetals hydrolyze faster than do the corresponding 6-membered ring acetals. But the situation is the reverse when the 5-membered ring and 6-membered ring ketals are compared.

Ceder's work shows the following order of stabilities towards

acid-catalyzed hydrolyses:



while on the other hand:



The differences in reactivities between the 5- and 6-membered rings are of the order of 10^1 .

In the present work, a qualitative comparison of the stability towards hydrogenolysis of 5- and 6-membered ring acetals and ketals gave the results shown in Table XIII.

It is seen that in all cases the 1,3-dioxolane acetals reacted faster than did the corresponding 1,3-dioxane acetals. The results were the opposite when the substances in question were the cyclic ketals.

A possible explanation is that for the 1,3-dioxane ketals, there are two $\text{CH}_3//\text{H}$ interactions, not present in the 1,3-dioxolane ketals (see below).

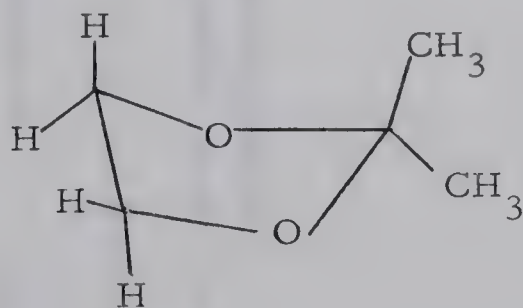
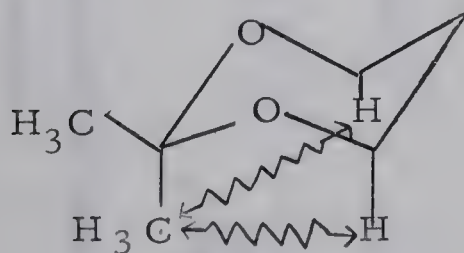


TABLE XIII

Competitive Reduction of Some Substituted 1,3-Dioxanes and 1,3-Dioxolanes.

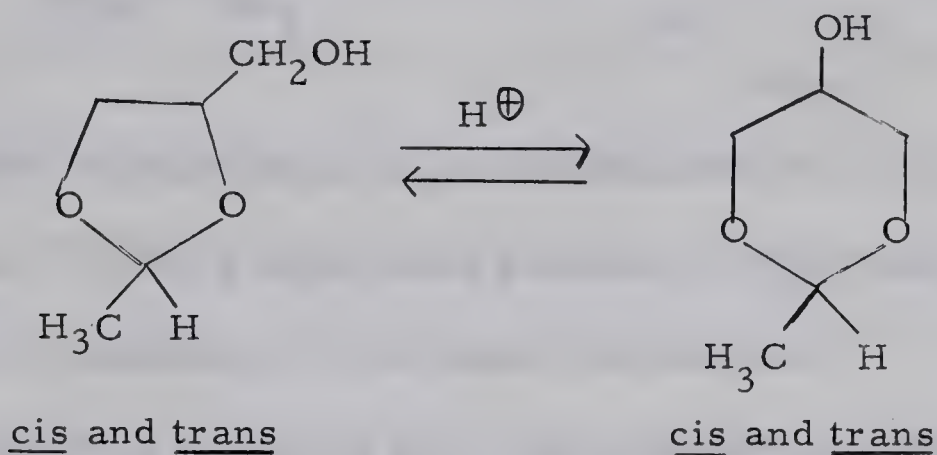
Expt. No. ^a	Compound Reduced		Time of Reduction, min.	Total Recovery, %	Extent of Reduction, %	
	1,3-Dioxane	1,3-Dioxolane			1,3-Dioxane	1,3-Dioxolane
1 ^b	2-phenyl-	2-phenyl-	20	89	30	100
2 ^b	2,2,4-trimethyl-	2,2,4-trimethyl-	20	73	92	41
3 ^c	2-methyl-	2-methyl-	120	70	0	66
4 ^c	4-methyl-	4-methyl-	120	80	0	40

a) In all cases the procedure described by Leggetter and Brown (1) was used, with the following proportions of reagents:

b) $\text{LiAlH}_4:\text{AlCl}_3:\text{acetal:acetal} = 1:1:1:1$

c) $\text{LiAlH}_4:\text{AlCl}_3:\text{acetal:acetal} = \frac{1}{2}:\frac{1}{2}:1:1$

Similar phenomena have been reported in the literature. Aksnes et al (58), studying the reaction between glycerol and acetaldehyde, established the existence of an equilibrium between the cis- and trans-2-methyl-4-hydroxymethyl-1,3-dioxolane and cis- and trans-5-hydroxy-2-methyl-1,3-dioxane.



The yield of the acetal isomers was found to be temperature dependent. At low temperatures the 1,3-dioxane system was favored. At 25°C, for example, during the first few minutes of the synthesis, the ratio 1,3-dioxolane/1,3-dioxane is $\gg 1$. After 70 minutes of reaction, the mixture reached equilibrium with the dioxolane/dioxane ratio of approximately 1:1 (See Fig. 7 below).

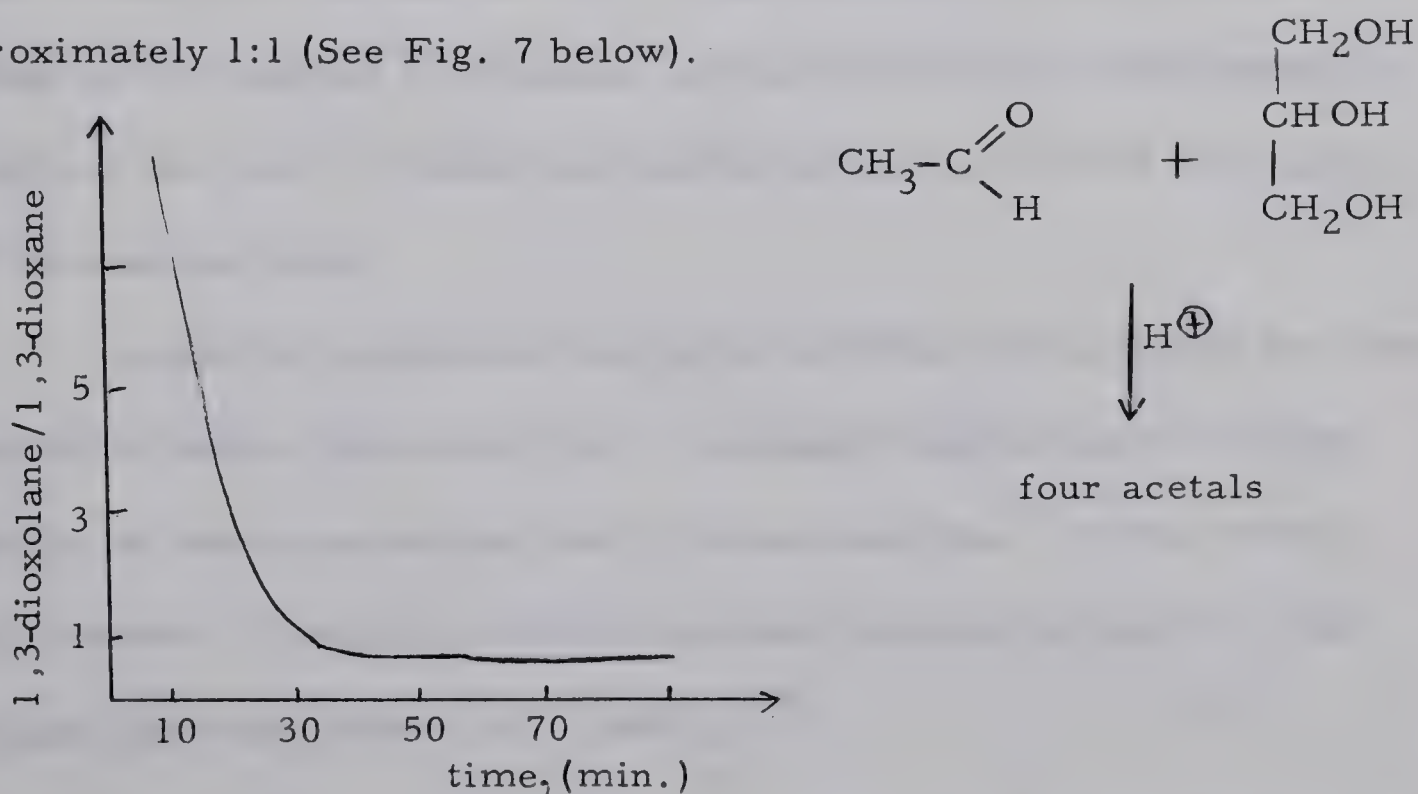
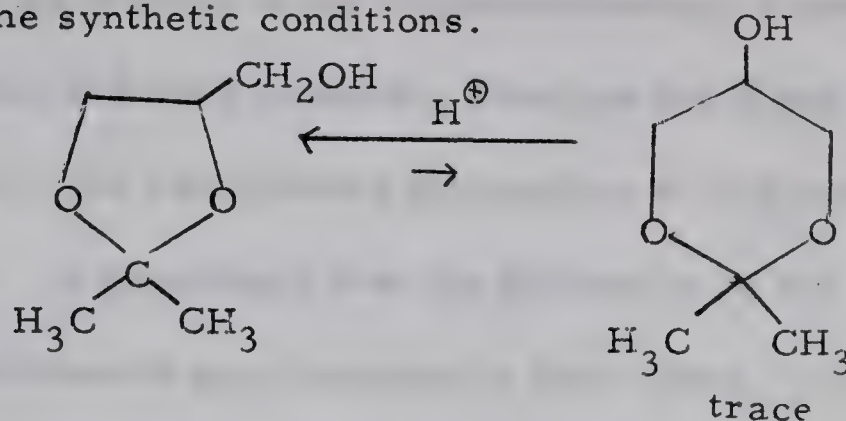


Fig. 7. Ratio of 1,3-dioxolane/1,3-dioxane isomers at different times during synthesis.

On the other hand, acetone and glycerol produced only the 1,3-dioxolane under the same synthetic conditions.



After isomerization of the 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane at -4°C for 4 days in the presence of HCl , only a trace of the 5-hydroxy-2,2-dimethyl-1,3-dioxane was detected

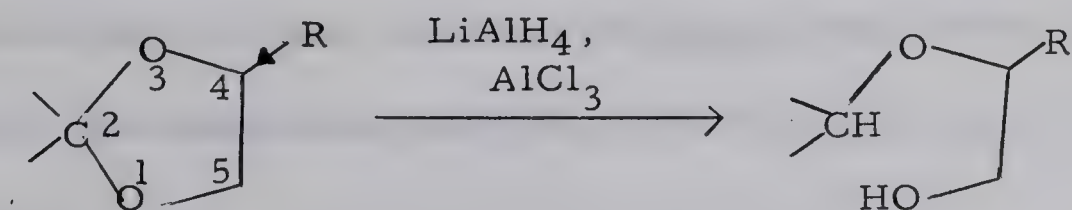
According to Aksnes *et al*, the explanation behind these facts is the introduction of an axial opposition of the C_2 methyl group and the hydrogen atoms at C_4 and C_6 in the 1,3-dioxane ring of the ketal. This repulsion is estimated by the authors to be about 2 Kcal/mole. By use of these values, calculation forecasted an equilibrium mixture containing about 97% of the dioxolane at 0°C . Experimentally it was possible to isolate in 2% yield the 1,3-dioxane isomer of the ketals after keeping a sample of the pure 1,3-dioxolane isomer in contact with an acid catalyst at 0°C for several days.

A similar explanation was given by Eliel (59) to justify the lower stability of ketals possessing the 1,3-dioxane ring compared with the stability of ketals possessing the 1,3-dioxolane ring. In the former there existed 1,3-diaxial repulsion between the alkyl group on C_2 and the axial hydrogen atoms on C_4 and C_6 .

XII. Anomalies Observed

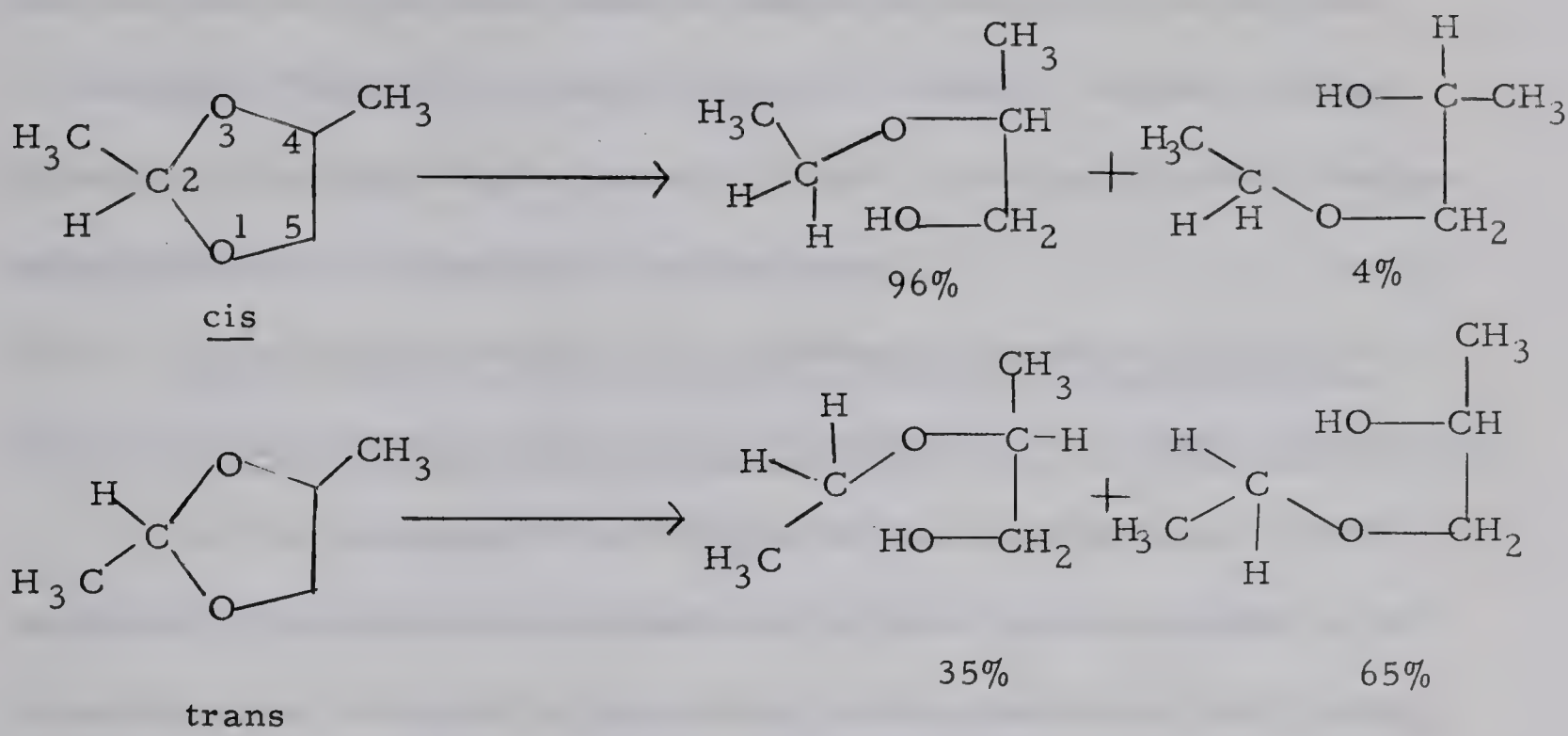
a) The cis isomer of the 6-methoxymethyl-2-methoxytetrahydropyran produces 60% ring cleavage, whereas the trans isomer gives 80% ring cleavage. No satisfactory explanation of this point can be offered at this stage. It is unlikely that the difference is due to polar factors since the substituents are the same in both cases. Undoubtedly, steric factors are responsible. At the moment the only suggestion which can be made is that in the case of the cis isomer, the ring oxygen, being more crowded than the side chain oxygen, is more difficult to approach by the Lewis acid, with a consequent decrease in the proportion of ring opening.

Anomalies of this type have been found also in the literature. Leggetter and Brown (44) studied the hydrogenolysis of cis- and trans-2,4-dimethyl-1,3-dioxolane and 2-ethyl-4-methyl-1,3-dioxolane and found that the direction of cleavage was different for the cis than for the trans isomer. According to their previous observations (1) an electron donor substituent at C₄ should favor cleavage of the -C₂-O₁- bond as shown.



This was so in practically all the cases studied. However, for

the cis- and trans-2,4-dimethyl-1,3-dioxolanes, the trans isomer showed a larger proportion of the secondary alcohol than expected. This is shown below.



Also it was found that the cis isomer was reduced about 7 times faster than was the trans isomer. Similarly, the cis isomer of the 2-ethyl-4-methyl-1,3-dioxolane was reduced 10 times faster than was the trans isomer. It is important to remember that this agrees with the findings of Salomaa (26) concerning the ratio of hydrolysis of these two isomers. Leggetter and Brown suggested that C_2-O_1 bond breakage can be considered "normal" and that for some reason in the trans isomer this C_2-O_1 cleavage is retarded. No explanation could be given as to the origin of this retardation.

By examination of Table IV, we can see similar anomalies concerning the hydrolysis rates of dioxanes and dioxolanes. 2-Phenyl-1,3-

dioxane show an increase in the rate of hydrolysis by a factor of 10^6 with respect to the parent compound (Table IV, entry 4). The introduction of a second phenyl group, however, does not produce the same increase; and the rate is of the same order of magnitude as the monosubstituted 1,3-dioxane (Table IV, entries 4 and 10).* A similar situation can be observed in the same Table, entries 3 and 9. We can not offer a reasonable explanation of these facts, at this stage.

XIII. The Reduction of Methyl 2,3,4,6-Tetra-O-methyl- α -D-glucopyranoside and Methyl 2-Deoxy-3,4,6-tri-O-methyl- α -D-glucopyranoside.

At the beginning of the program of work in this thesis, some exploratory experiments were made on the above title compounds to try to establish the behaviour of glycosides towards reductions with LiAlH_4 / AlCl_3 . Due to the difficulties encountered during the hydrogenolysis of these fully methylated glucosides it was decided to study first the simplified model compounds as presented in this thesis. This work on the reduction of glycosides was not resumed but some pertinent observations from the results obtained can be presented at this time.

The knowledge gathered from reduction of the homologous model compounds will be a useful guide in planning a future study of the hydrogenolysis of the glycosides.

Attempts at Reduction of the Permethyated D-Glucose.

Because of the poor solubility of methyl α -D-glucopyranoside in ether and since the free hydroxyl groups could consume much of the

* In fact there was a slight decrease in rate.

LiAlH_4 , the fully methylated homologue was selected as the substance to be hydrogenolyzed. Several attempts in this direction showed that over a period of 18 to 24 hours no hydrogenolysis was apparent. Only the original material was recovered to the extent of 80 to 90%.

When the reaction was allowed to proceed for 72 hours and the analysis of the products done by gas liquid chromatography, three small peaks of approximately equal intensity were observed, following the large main peak corresponding to the starting material. As well, a trace of the β isomer of the starting material was observed.

The infrared spectrum of this mixture of products showed strong absorption in the 3μ region, indicative of hydroxyl groups. This mixture was then remethylated and the product subjected again to analysis by gas liquid chromatography. Now, only two peaks were observed in the chromatogram, the second of which corresponded in retention time to that of the starting material (pentamethyl glucose). This peak comprised 95% of the remethylated product. The retention time of the first peak was compared with those corresponding to authentic samples of tetramethylpolygalitol (85) and hexamethylsorbitol (85) the two substances which might be expected from this hydrogenolysis. The retention time for the unknown peak (which appeared first in the chromatogram of the remethylated product was identical to that found for hexamethylsorbitol, thus indicating that hydrogenolysis occurred by way of ring cleavage.

The identity of the three peaks obtained from the hydrogenolyzed

glucoside, before remethylation was not determined. However since upon remethylation, only one peak in addition to that for the starting material was obtained, it is likely that under the conditions of reduction, cleavage of one or more of the $-\text{OCH}_3$ groups of the pentamethyl glucoside had occurred. Remethylation of the cleavage product would produce pentamethyl glucoside.

Attempts of Reduction of Methyl 2-Deoxy-3,4,6-tri-O-methyl- α -D-glucopyranoside.

Since methyl 2,3,4,6-tetra-O-methyl- α -D-glucopyranoside is one of the glycosides which hydrolyzes with relatively great difficulty (61) and since there appears to be a strong parallel between hydrogenolysis and hydrolysis, a more reactive glycoside was chosen. The relatively high rate of hydrolysis of the 2-deoxyglycosides suggested that methyl 2-deoxy-3,4,6-tri-O-methyl- α -D-glucopyranoside would be more suitable. The two possible products from the hydrogenolysis of the last compound can be seen in Chart 47.

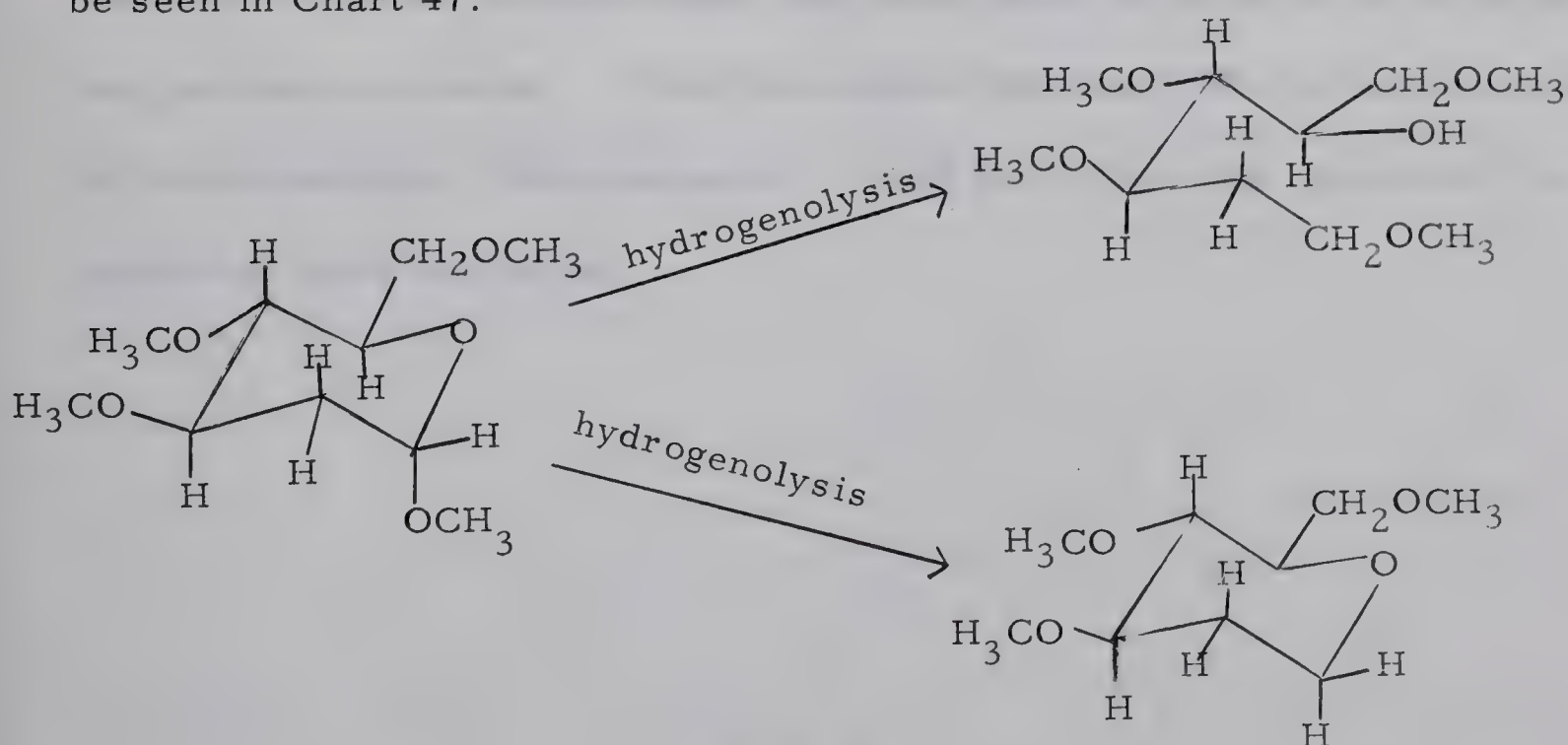


Chart 47

Reduction of the fully methylated 2-deoxyglucose for 24 hours afforded a mixture of products which gave by gas chromatography analysis a pattern similar to that obtained for the pentamethyl α -D-glucoside.

The chromatogram showed a large peak corresponding to the starting material, and three additional peaks, present in a ratio 1:5:2.

These last three peaks together represented 45% of the total reduction product, and thus showed that the 2-deoxyglucoside had indeed reacted more readily than did the pentamethyl α -D-glucoside. Remethylation of this mixture and subsequent gas chromatography analysis gave only two peaks, one corresponding to the original material and a second peak replacing the three found before methylation. This new peak was present in the mixture to the extent of 20% and has not yet been identified.

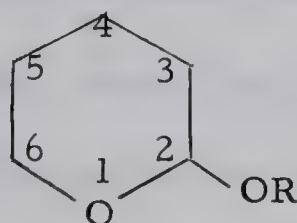
By analogy with the pentamethyl α -D-glucoside above, this could be 2-deoxypentamethylsorbitol. The information gathered up to now from this work with the two glucosides mentioned does not allow us to establish any general conclusion. From the results obtained from the hydrogenolysis of the pentamethyl α -D-glucoside it would seem that ring opening is the preferred route of reaction.

APPENDIX

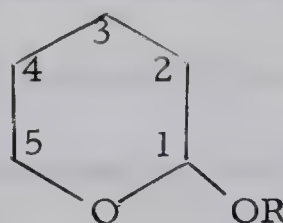
Polar versus Steric Effects on the Rate of Hydrolysis of Glycopyranosides.

In the light of the information obtained from the hydrogenolysis of the simpler homologues of the glycopyranosides, and assuming that the features affecting the rate of hydrogenolysis similarly affect the rate of hydrolysis, it is now of merit to examine some aspects of the problem of hydrolysis of glycopyranosides.

From the determination of the rate of hydrolysis of a large number of glycosides it is known that a substituent on C_2 (C_3 in the tetrahydropyran system) is a major rate-determining factor. For example,



Tetrahydropyran
system



Pyranoside
system

if we examine the hydrolysis rates of some isomeric methyl pyranosides (61), (Table XIV, page 117) we can see that the replacement of an -OH group on C_2 by an hydrogen atom introduces a dramatic change in the speed of hydrolysis. Whereas changes in configuration about C_2 or about any of the other carbon atoms in the ring result in rates which differ from each other only by units, substitution of -OH by -H at C_2 increases the rate by a factor of thousands, (Table XIV, entry 7). The effect of changes at

C₅ (e.g. replacement of the -CH₂OH group by CH₃ or by H (Table XIV, entries 5, 9) makes only a 10- to 20- fold difference in rate. These examples indicate that polar effects seem to produce much greater changes than do steric factors.

An attempt has been made by Feather and Harris (61) to explain the differences in rates of hydrolysis of the glycopyranosides on the basis of the following factors: 1) Interaction between substituents on carbons 2 and 3 and also between substituents on carbons 4 and 5. 2) The anomeric effect (43), and 3) the Reeves' effect (48). The first of these is given the greatest significance and therefore will be discussed first.

These authors postulate a direct relationship between (a) the ease of rotation about the C₂-C₃ and C₅-C₄ bonds, to allow the molecule (pyranoside) to assume the semi-chair conformation, and (b) the rate of hydrolysis. The ease of rotation depends not only on the extent of interaction between the groups on C₂ relative to those on C₃ and on C₄ relative to those on C₅ but also on 1,3-diaxial interactions. Feather and Harris placed special emphasis on the ease of rotation about the C₂-C₃ bond and about the C₅-C₄ bond. According to these authors, data in Table XIV, "show that the rate is decreased by increased opposition of substituents on C₂, vis-a-vis those on C₃ when rotation is in the direction which tends to eclipse the equatorial groups". The same statement applies to C₅-C₄ rotation.

Edward (62) in 1955 used almost the same words to describe this

TABLE XIV

Hydrolysis Rates of Some Anomeric Methyl Pyranosides. *

Methyl Pyranoside of:	Entry	Relative Rate	Stable Conformation	Orientation of Methoxyl**
α -D-Glucose	1	1.0	C1	a***
β anomer		1.9	C1	e
α -D-Mannose	2	2.4	C1	a
β anomer		5.7	C1	e
α -D-Galactose	3	5.2	C1	a
β anomer		9.2	C1	e
α -D-Xylose	4	4.5	C1	a
β anomer		9.1	C1	e
α -L-Rhamnose	5	18.3	1C	a
β anomer		19.0	1C	e
α -D-Glucuronic acid	6	0.47	C1	a
β anomer		0.62	C1	e
2-Deoxy- α -D-glucose	7	2090	C1	a
β anomer		5125	C1	e
2,3,4,6-Tetra-O-methyl- α -D-glucose	8	0.16	C1	a
β anomer		0.4	C1	e
α -L-Arabinose	9	19.0	C1	e
β anomer		13.1	C1	a

*Taken from the work by Feather and Harris (61).

**Anomeric methoxy group

***a = axial; e = equatorial

phenomenon. He stated "the ease of the change* will be affected by the configuration and degree of substitution on C_2 , C_3 , C_4 and C_5 as follows: It will be hindered by the increased opposition of substituents on C_2 vis-a-vis those on C_3 , and on C_5 , vis-a-vis those on C_4 , produced by the rotation mentioned above". This is illustrated in Chart 48.

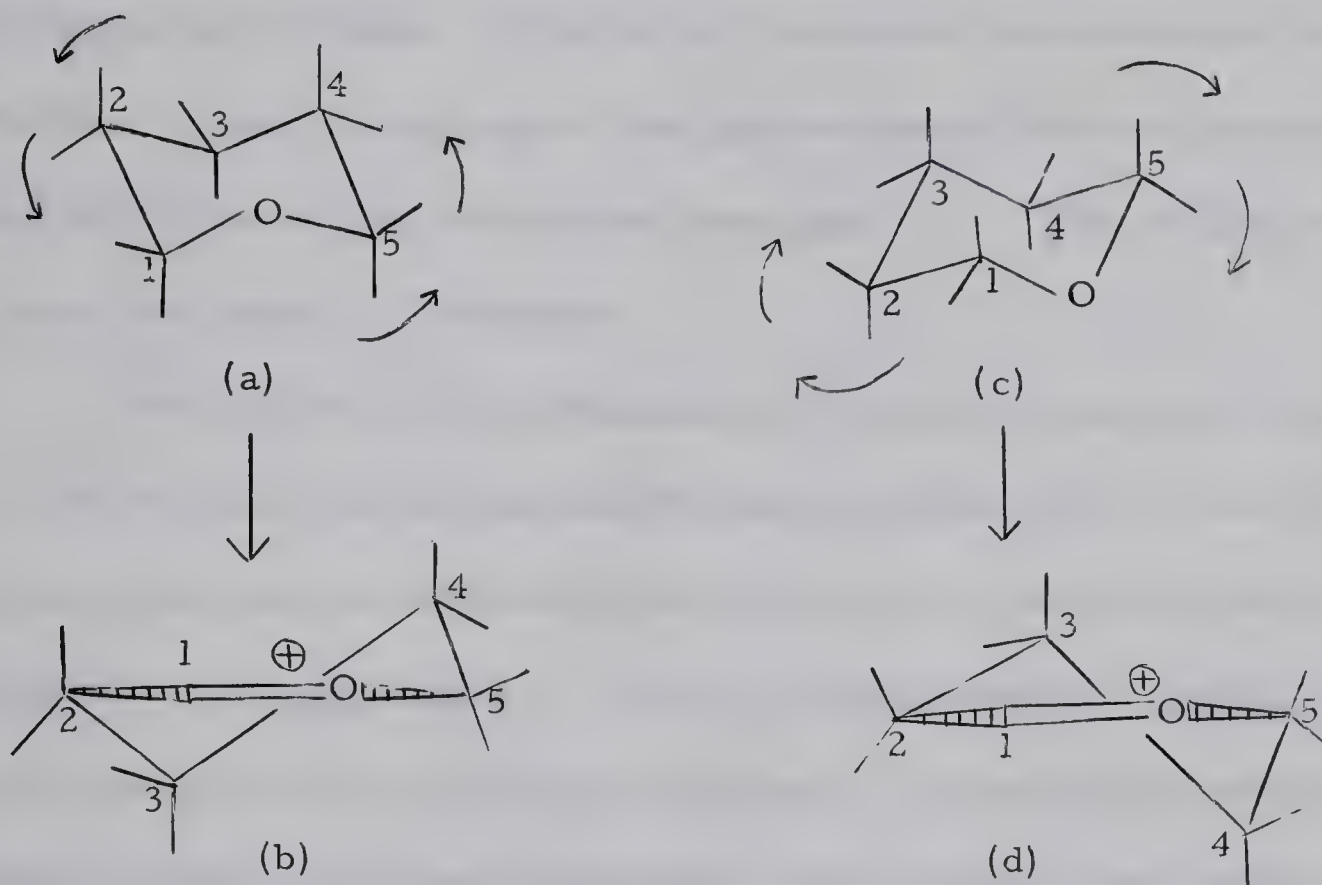


Chart 48

He also pointed out that the resistance to rotation will increase with the increased size of the substituents. In this way the following order of stabilities to hydrolysis is explained:

a) heptosides $>$ hexosides $>$ pentosides,

b) normal sugars (pyranosides) $>$ 3-deoxypyranosides $>$ 2-deoxypyranosides $>$ 2,3,-dideoxypyranosides.

* that is, to go from the chair to the semi-chair conformation.

The same order of stabilities is shown by Feather and Harris (61) In addition these authors present the following sequence within the pyranosides ,
 D-glucosides > D-mannosides > D-galactosides > D-xylosides > D,L-arabinosides.

A careful reexamination of the steric evidence for the above conclusions is revealing. First of all, the above considerations imply that hydrolysis occurs by cleavage of the aglycon group (with ring retention), according to the A-1 (A) mechanism (see page 31). This we believe has not been conclusively established.

The results we have obtained from the hydrogenolysis of the 3- and 6-substituted-2-alkoxy(aryloxy)tetrahydropyrans show quite clearly that one of the factors involved in the direction of cleavage is the type of R attached to the exo oxygen. As well, substituents at C₃ and C₆ have an effect on the preferred route of cleavage. If a parallel is assumed between hydrogenolysis and hydrolysis, then it is quite conceivable that the mechanistic pathway for hydrolysis of glycopyranosides also depends upon the nature of the aglycon group and the substituents at C₅ and C₂ (numbering for the glycopyranoside ring). If ring cleavage occurs in some cases, it follows that in those instances the problem of ease of attainment of the semi chair form does not enter. For example for a methyl glycoside with an hydroxymethyl group at C₅, two different oxo-carbonium ions can be formed from the protonated molecule during hydrolysis (Chart 49 (a) and (b)).

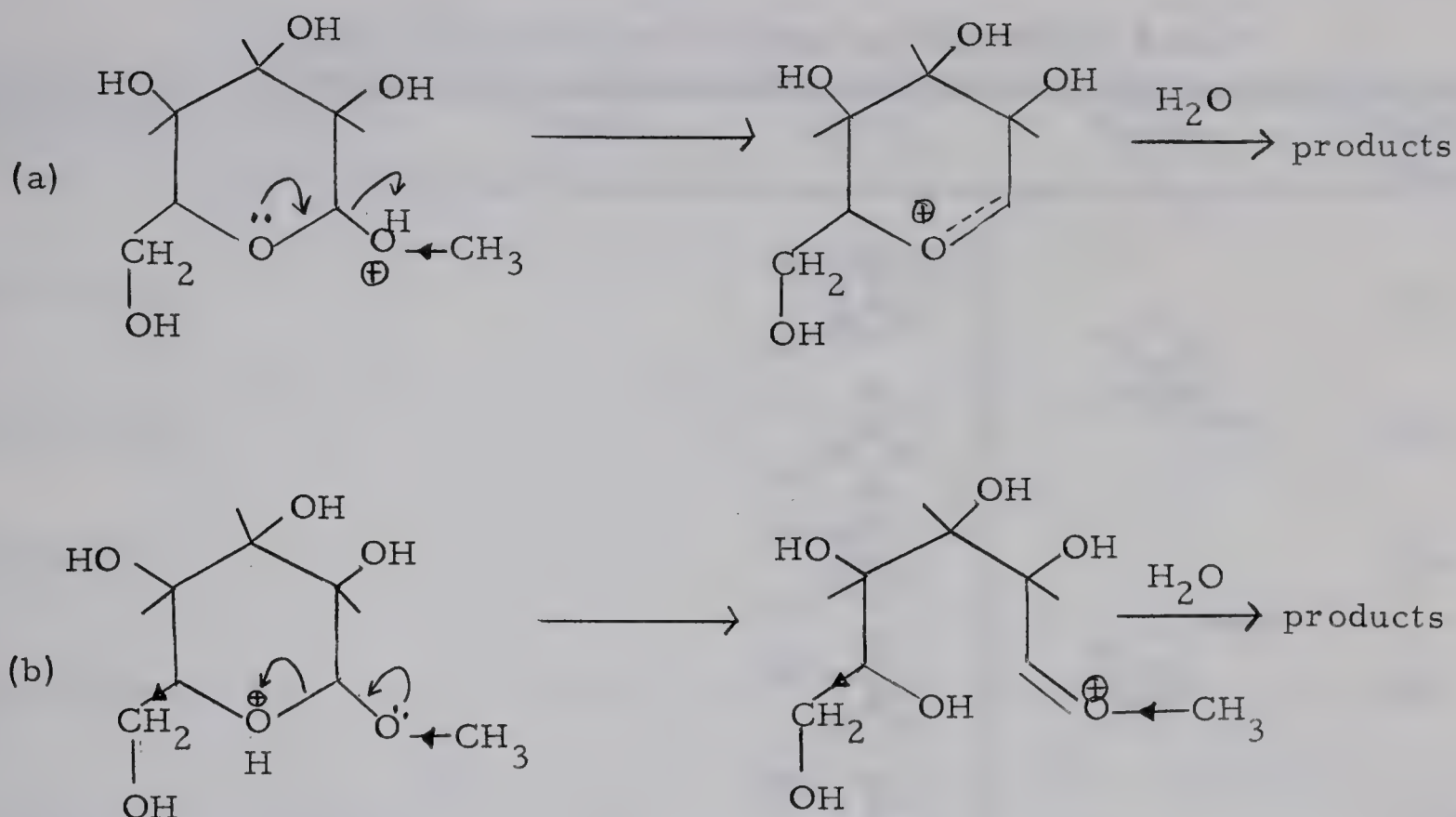


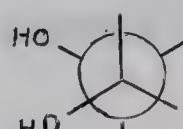
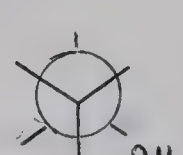
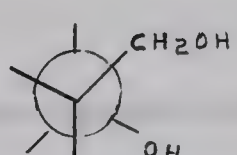
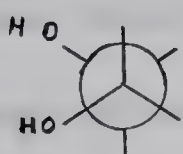
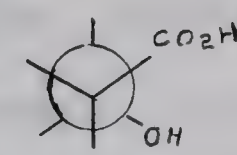
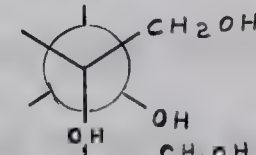
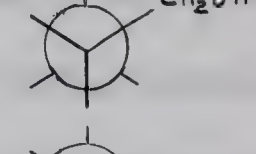
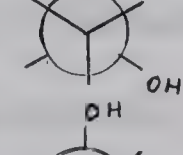
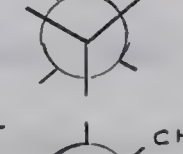
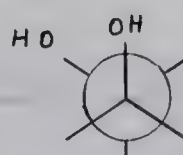
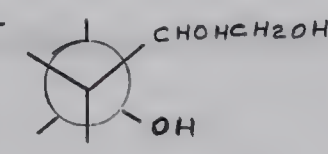
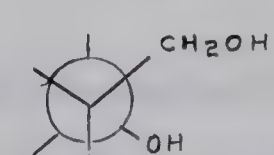
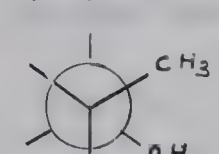
Chart 49

In case (a) there is an electron attracting group (HOCH_2-) vicinal to the ring oxygen, and this group destabilizes the positive charge in the oxocarbenium ion. In case (b), the exo-oxygen stabilizing the positive charge is attached to an electron donating group, $-\text{CH}_3$. Consequently it is reasonable to assume that the second carbonium ion will be more stable than is the first one. Hence we would expect preferential ring opening.

However assuming that the formation of this intermediate cyclic carbonium ion does actually occur, the conclusions made by Feather and Harris concerning the ease of rotation about C_2-C_3 and C_4-C_5 bonds is open to criticism. Referring to the structures in Table XV, page 121, when the molecule approaches the semi-chair conformation to form the cyclic oxocarbenium ion, C_1 will change from tetrahedral geometry to a

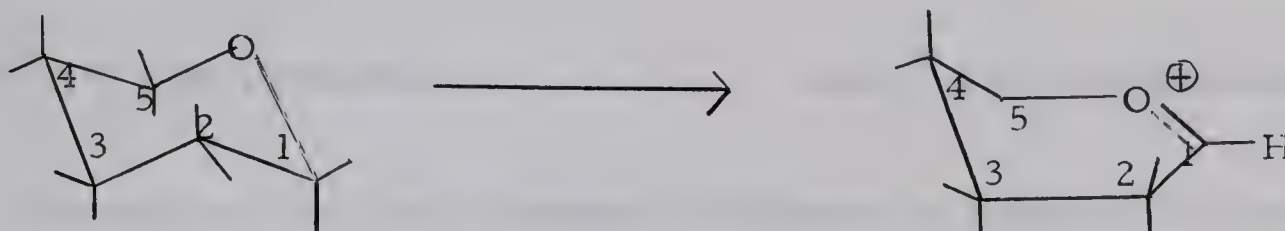
TABLE XV

The Effect of the Glycosyl Group on Hydrolysis Rate.*

Methyl Pyranoside of:	Entry	C ₂ -C ₃	C ₅ -C ₄	Relative Rate
β -D-Xylose	1			9.1
β -D-Ribose	2			12.3
β -D-Glucose	3			1.9
β -D-Mannose	4			5.7
2-Deoxy- β -D-glucose	5			5.125
β -D-Glucuronic acid	6			0.62
β -D-Glucose	7			1.9
β -D-Galactose	8			9.2
β -D-Xylose	9			9.1
α -L-Arabinose	10			13.5
β -D-Glycero-L-manno-heptose	11			3.2
β -D-Mannose	12			5.7
β -D-Rhamnose	13			19.0

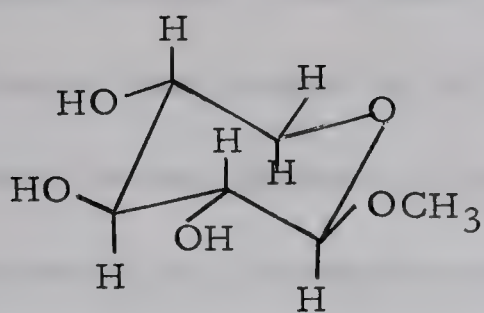
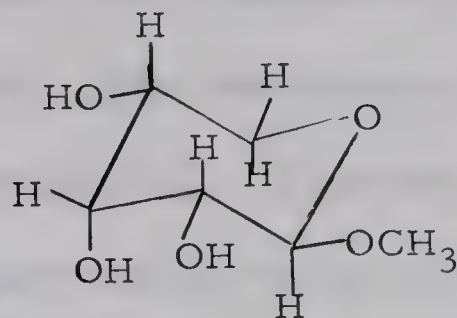
* Taken from the work of Feather and Harris (61).

planar trigonal form (Chart 48). This requires C_2 , C_1 , O and C_5 to be in one plane, with C_3 beneath (above) the plane and C_4 above (below) it. Sometimes this form is represented with C_3 also coplanar with C_2 , C_1 , O and C_5 , leaving only C_4 above the plane (63), as shown below.



In order to attain the semi-chair form, C_2 moves downwards with a counterclockwise motion as shown by the arrows shown in Chart 48((a) to (b)), and C_5 moves upwards with counterclockwise motion*. This mechanical action has been corroborated by actual use of Dreiding models. Accordingly during this process the equatorial substituent on C_2 moves away from any equatorial substituent on C_3 . On the other hand if we had an axial substituent on C_3 , as in β -D-ribose, Table XV, page 121 anti-clockwise rotation of C_2 would tend to bring the equatorial group on C_2 closer to the axial -OH on C_3 , resulting in a dihedral angle of about 40° between the two -OH groups in the semi-chair conformation. This is illustrated below using the most probable C1 conformation of the methyl pyranoside structures of β -D-xylose and β -D-ribose as examples.

* The observer sights along the C_2 - C_3 and C_5 - C_4 bond, in that order:
e.g. $2 \rightarrow 3$; $5 \rightarrow 4$.

methyl β -D-xylopyranosidemethyl β -D-ribofuranoside

Since the C_5-C_4 environment is the same in both structures, this part of the molecule can be ignored. Now, writing the Newman projection for C_2-C_3 and C_5-C_4 bonds, we have the following situation in tabular form.

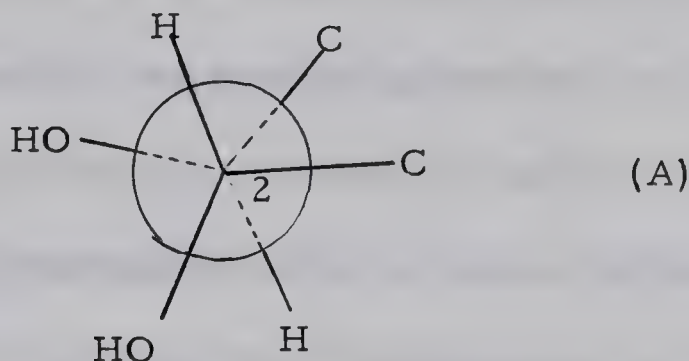
Methyl pyranoside of	C_2-C_3	C_5-C_4	Relative rates* of hydrolysis
β -D-Xylose			9.1
β -D-Ribose			12.3

* Rate for methyl α -D-glucopyranoside = 1(relative).

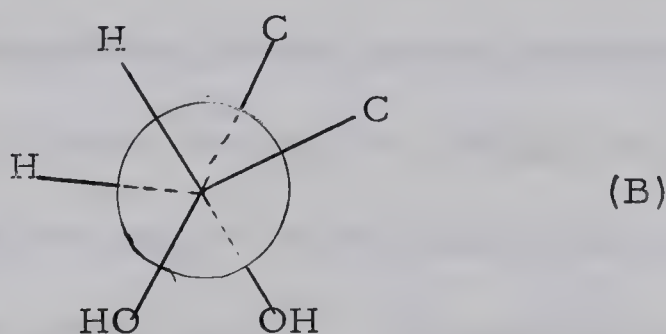
If we consider methyl β -D-xylopyranoside we begin with a gauche interaction between the two -OH groups, that is often symbolized as HO/HO (64).

In rotating C_2 counterclockwise as shown by the arrow in the above illustration we are relieving the OH/OH interaction and we are creating two quasi OH/H interactions. These two interactions can be considered to be

negligibly small, less than 0.1 Kcal/mole each (48), whereas an HO/HO interaction has a value of 0.35 Kcal/mole (48). The new dihedral angle between the two hydroxyl groups is approximately 80° . This new conformation about the C_2-C_3 atoms for methyl β -D-xylopyranoside can be represented as shown in A (below).



With the methyl β -D-ribopyranoside we begin with an OH/OH interaction, and as the C_2 rotates we now create one quasi HO/HO interaction and one quasi H/H interaction as illustrated in B.



From the observations of the two projections, A and B we have for the xyloside two quasi H/OH interactions, for the riboside one quasi HO/HO and one quasi H/H interaction. Since the interaction between an hydrogen atom on one carbon and any group on the adjacent carbon is believed to be practically zero (48), it is clear that the second situation is going to be more difficult to achieve than the first, and accordingly the hydrolysis of methyl β -D-ribopyranoside should be a slower process than is that of methyl β -D-

xylopyranoside. The experimental results are the opposite. The relative rates are 12.3 and 9.1 respectively (Table XV, entries 1 and 2).

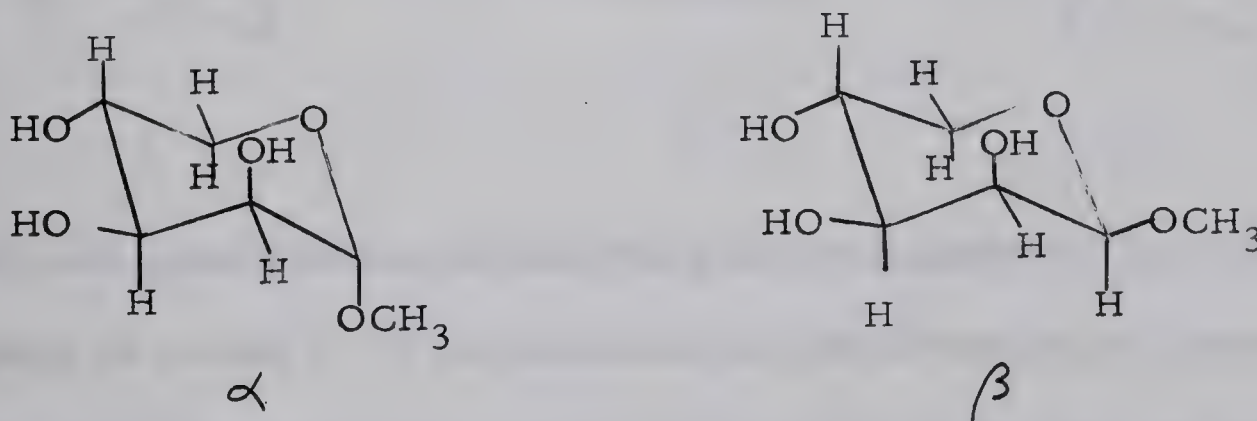
The same arguments can be used in the case of the methyl pyranosides of β -D-glucose and β -D-mannose (Table XV, entries 3 and 4). Rotation of C_2 should be more difficult in the case of the mannoside. However, the mannoside hydrolyzes faster than does the glucoside, the relative rates being 5.7 and 1.9 respectively (Table XIV, entries 2 and 1).

The rest of the examples lead to the same findings. Accordingly from the above analysis it is clear that the statement by Feather and Harris that there is a direct relationship between the ease of rotation about C_2-C_3 and C_5-C_4 , and the reactivity towards acid hydrolysis, is not, we think based on firm grounds, and certainly is not generally valid. The other effects, mentioned by Feather and Harris are the anomeric effect and the Reeves' effect. Due to the first of these two influences, alkoxy, acyloxy and halogen groups prefer the axial over the equatorial orientation when at the anomeric center of an aldopyranose. The greek letter " α " is used to designate this effect (64, 65).

Because of this influence β anomers should be more reactive than the α anomers; and according to Feather and Harris, the orientation of the aglycone, equatorial or axial, is a rate determining factor. Generally, β isomers hydrolyze more rapidly than do the α isomers as the data in Table XIV show. This was pointed out by the authors but no detailed explanation as to the nature of the effect was given by them. A comprehensive

study of this effect was given by R. U. Lemieux in 1965 (65). The difference in rate brought about by this effect is of the order of units (e.g., a factor close to 2, Table XIV). The energy for this effect is estimated to be 1.5 to 2 kcal/mole(65).

Because of the second influence (Reeves' effect) a chair conformation is under great strain when it has an axial hydroxyl group in position 2, as well as an hydroxyl or alkoxy group in the equatorial position at C_1 . This effect has been termed $\Delta 2$. The energy for this effect is estimated to be about 1 Kcal/mole (65). According to Feather and Harris, the high rate of hydrolysis of the methyl pyranoside of β -D-lyxose (relative rate 46.4) as compared with the α isomer (relative rate 14.5) is explained in terms of both the presence of an equatorial methoxy group at C_1 (the anomeric effect) and the $\Delta 2$ factor. The structures of α and β -methyl D-lyxopyranosides are shown below.

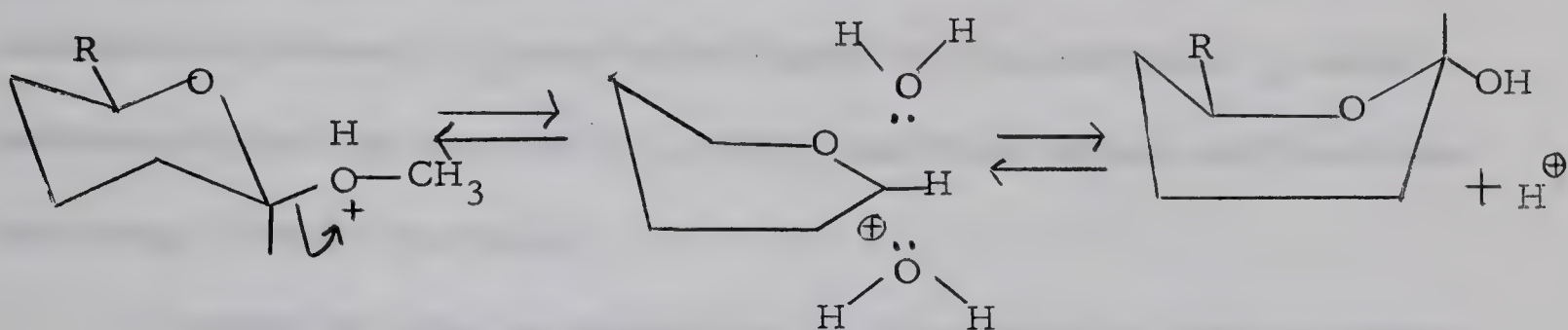


Methyl D-lyxopyranoside

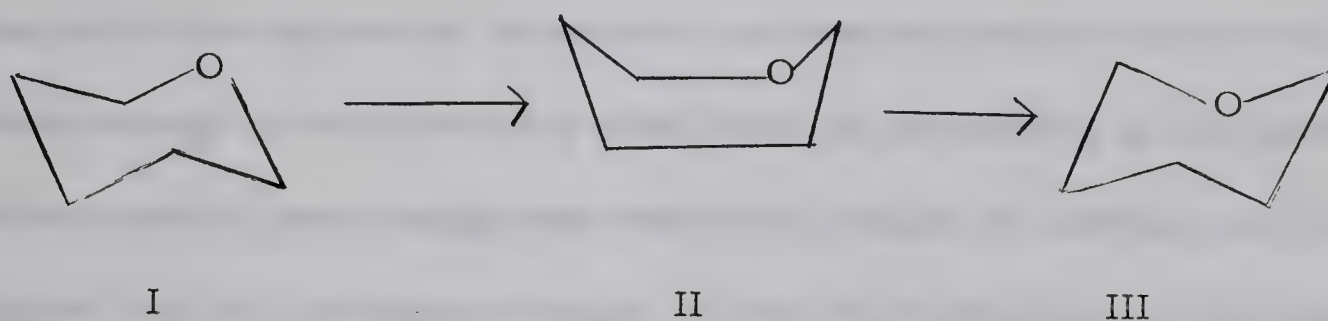
Feather and Harris did not define the mode of action of the $\Delta 2$ factor on the rate of hydrolysis.

Foster and Overend (63) also considered the pyranoside conformation

as a major cause of the differences in the rates of hydrolysis of the pyranosides. They did not talk, however, in terms of rotation about the C_2-C_3 and C_5-C_4 bonds. The main effects, according to them, are the configuration at the glycosidic center (i.e. β -anomers hydrolyze faster than do the α -anomers) and the increase in the number of non-bonded interactions when the molecule assumes the semi-chair conformation.



This change is similar to the conformational oscillation $I \longrightarrow III$, and it



will meet great resistance when the preferred conformation of the molecule is such as that in I. This resistance will be a maximum in such molecules as methyl α -D-glucopyranoside, in which all of the groups (excluding that at the anomeric center) occupy the equatorial position.

As the number of axial groups in the preferred conformation increases, the difficulty of conversion from I to II decreases. The authors assume here that the molecule will go eventually, completely to the boat

conformation, a situation which is not necessarily so.

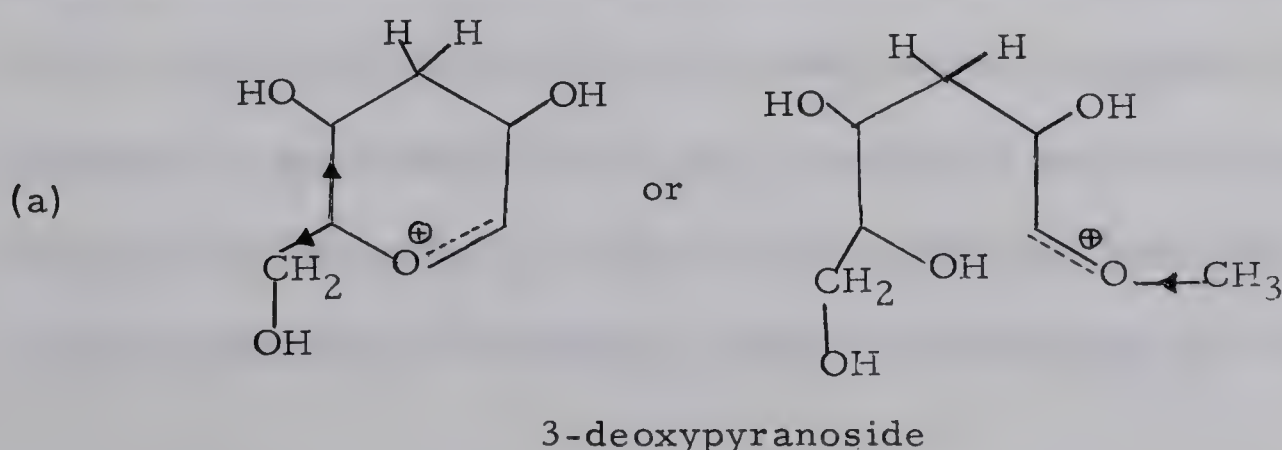
The fact that a molecule with a large number of axial substituents will be more unstable than a molecule with all the substituents equatorial and will undergo faster hydrolysis was explained by Edward (62) relating the ease of hydrolysis to the ease of change from the chair to the semi-chair conformation. According to this line of reasoning when the oxo-carbonium is formed, C₂ axial substituents will recede from C₄ axial substituents and the same for C₃ and C₅; and these effects will facilitate the change already mentioned.

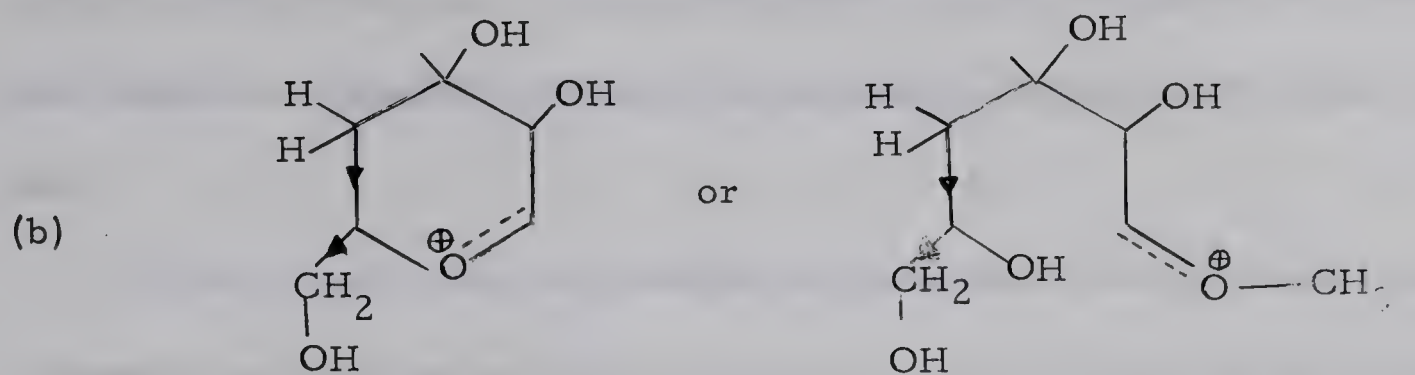
It should be noted as pointed out by Overend *et al* (66) that sometimes changes in reactivities are a consequence of changes in the entropy of activation. "Fairly small differences in reactivity often result from changes in the entropy of activation, so that the idea of relief of repulsive strain energy in the transition state must be something of a simplification." Unfortunately, even though the observed changes in entropy quite clearly support the A-1 mechanism (page 31) for the hydrolysis of glycopyranosides, they don't allow a differentiation between the cyclic and open chain mechanism. This can be understood considering ΔS^\ddagger as a measure "of the difference in the restriction on the freedom of motion in the ground and the transition state" (66). In a bimolecular reaction the reactants become more ordered as they reach the transition state with a consequent decrease in entropy and ΔS^\ddagger will therefore be negative. In a unimolecular reaction the reverse is true, with a positive ΔS^\ddagger .

Shafizadeh (67) in 1955 proposed that less activation energy is required when the initial free energy is higher. And of course, the higher the strain, the higher the free energy. This author used this kind of argument to support the A-1 (B) mechanism. But, in fact, the relief of strain could be achieved by either mechanism, A-1 (B) or A-1 (A).

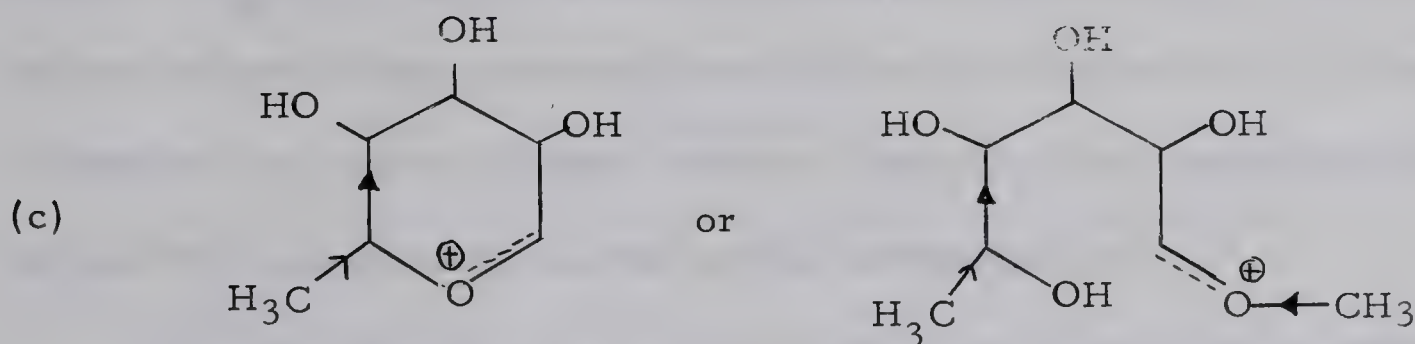
The major factor which will decide the pathway, we think, is the polar effect which stabilizes or destabilizes the oxocarbenium ion. As mentioned before, data in Table XIV show that differences in rates of hydrolysis of the various glycopyranosides are not pronounced except for the 2-deoxyglucopyranoside (α and β). These relatively small effects have been attributed to steric factors. If this is so it is very difficult to explain on these grounds the extremely high reactivity of the 2-deoxy sugars.

By making use of the inductive effects we can explain the relative rates of the glycosides shown in Table XVI, page 132. This is possible if we accept the view that the low reactivity of the ordinary sugar compared with that of the 2-deoxy sugars is due to the electron-withdrawing effect of the -OH group attached to C₂, thus destabilizing a positive charge at the anomeric center. The intermediate carbonium ions obtained by ring cleavage or by ring retention are shown in Chart 50.





4-deoxypyranoside



6-deoxypyranoside

Chart 50

We see that a 3-deoxypyranoside has the deoxy carbon two atoms removed from the positive center in either of the possible carbonium ions shown (Chart 50 (a)), and by inspection of these two ions, it is clear that the acyclic one should be the more stable.

The hydrolysis rate of the methyl 3-deoxy- α -D-glucopyranoside is only 20 times that of the parent compound, methyl α -D-glucopyranoside. Hence replacement of the electron withdrawing -OH group on C₃ by H results in a much milder increase in the rate of hydrolysis compared to that obtained when the C₂ -OH group is replaced by hydrogen. The faster rate of hydrolysis of the methyl 3-deoxy- α -D-glucopyranoside compared

to that of the methyl α -D-glucopyranoside can be explained as a removal of a destabilizing factor affecting the formation of the intermediate carbonium ion.

If we inspect the two possible oxocarbenium ions derived from the 4-deoxypyranoside we see that C₅ has now only one electron attracting group (-CH₂OH); C₄ has become a methylene group (CH₂). The deoxy carbon is three atoms removed from the positive charge at C₁ in the acyclic carbonium ion, and two atoms removed from the ring oxygen stabilizing the positive charge at C₁, in the cyclic carbonium ion.

Remembering that the acyclic carbonium from the 3-deoxypyranoside is probably the more stable one, and comparing it with the two possible ions derived from the 4-deoxypyranoside, we see that both sets of ions (cyclic and acyclic in each set) have similar stabilities. The experimental result shows that methyl 4-deoxy- α -D-glucopyranoside hydrolyzes twice as fast as the 3-deoxy homolog. According to the work by Overend et al (66), changes in the entropies of activation of the order of 4 e.u. bring about differences in rates of the order of 10¹ or less. It could be possible that a small difference in the entropy of activation might be the cause of the difference in reactivity, but no data could be found to substantiate this.

Finally, inspecting the oxocarbenium ions produced from the 4-deoxy- and 6-deoxypyranosides we see that in both cases, the acyclic one should be the more stable one; (the cyclic carbonium ion, has the positive ring oxygen attached to an electron withdrawing group, -CH₂OH for the 4-deoxy,

C_4HOH for the 6-deoxy). If we compare now the two acyclic carbonium ions in b and c, in the case of the 4-deoxyglucopyranoside the deoxy carbon is three atoms removed from the positive charge at C_1 , while in the 6-deoxy pyranoside the deoxy carbon is four atoms removed from the positive charge.

We would expect the 4-deoxy sugar to be the more reactive one and this is the case as found experimentally (Table XVI, entries 4 and 5).

TABLE XVI

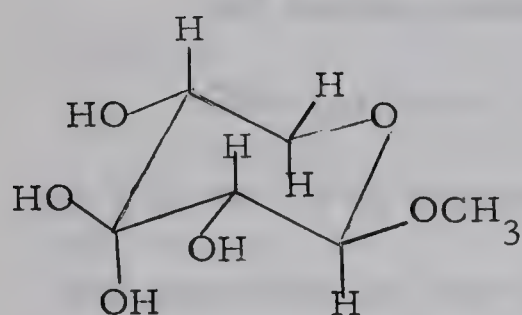
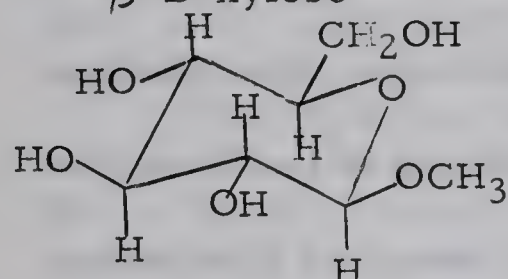
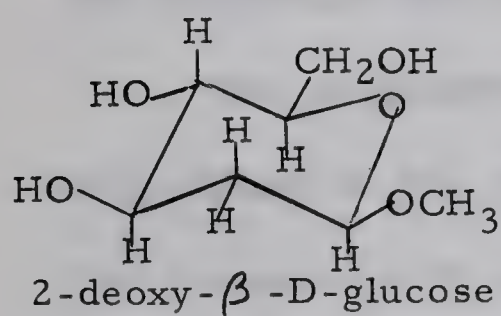
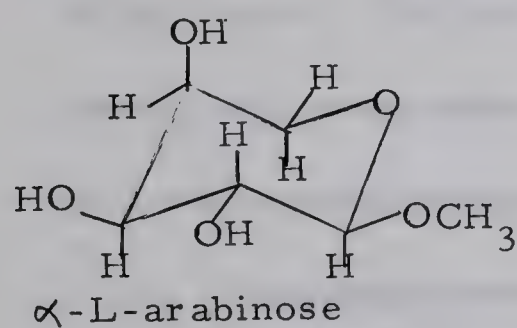
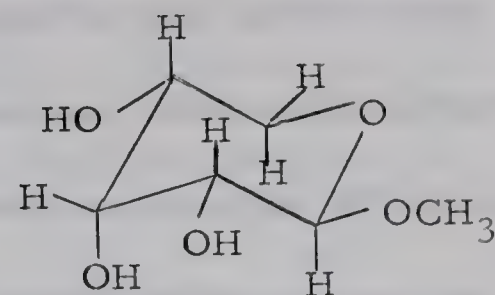
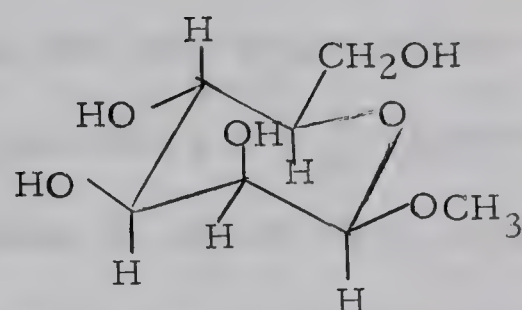
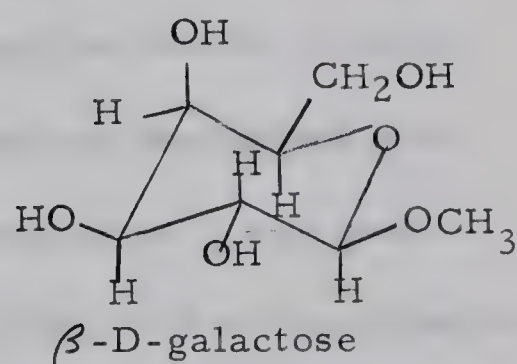
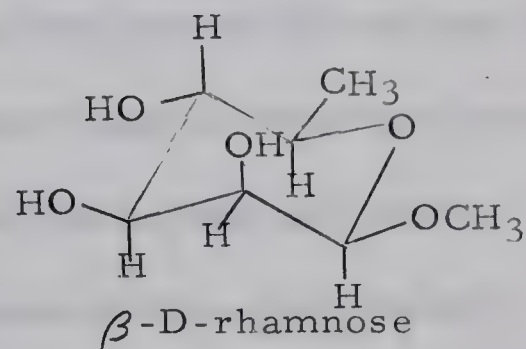
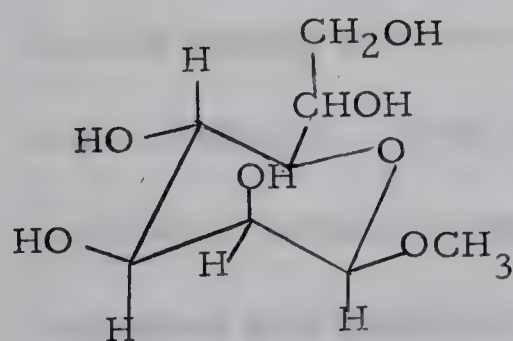
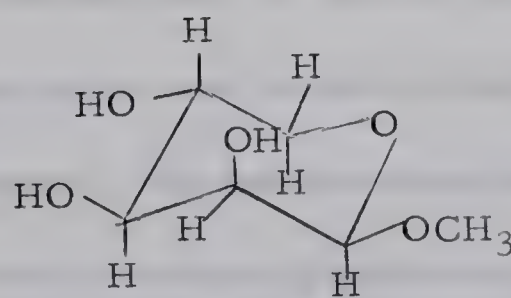
Relative Rates of Hydrolysis of Some Deoxypyranosides.

Methyl pyranoside of:	Entry	Relative rate	Reference
α -D-Glucose	1	1	66
2-Deoxy- α -D-glucose	2	2090	66
3-Deoxy- α -D-glucose	3	20	66
4-Deoxy- α -D-glucose	4	40	66
6-Deoxy- α -D-glucose	5	5	68
α -D-Mannose	6	2.4	67
6-Deoxy- α -L-mannose	7	10	67

In Table XVII the structures of some pyranosides mentioned in Table XIV are shown:

TABLE XVII

Structures of Some Methyl Pyranosides of:

 β -D-xylose β -D-glucose2-deoxy- β -D-glucose α -L-arabinose β -D-ribose β -D-mannose β -D-galactose β -D-rhamnose β -D-glycero-L-manno-heptose β -D-lyxose

EXPERIMENTAL

All boiling points and melting points reported are uncorrected.

The gas liquid chromatography analyses were made with a Burrell K-2 Kromo-Tog equipped with a 2-meter column packed with 20% butane-diol succinate on Gas-Chrom P, 60-80 mesh, using helium as carrier gas at a flow rate of about 70 ml per minute. Gas chromatography analyses were also done, particularly during the later stages of this work with an F and M machine, Model 700, equipped with a $6' \times \frac{1}{4}"$ column, packed with carbowax 20 M, 20% on Gas-Chrom P, 60-80 mesh, at a helium flow rate of 50 ml/min. Frequently the analyses were made using both machines, for the purposes of cross-checking the results obtained.

For preparative gas liquid chromatography, an Aerograph Auto-prep, Model A-700, Wilkens Instrument and Research Co., was used. The column was $20' \times \frac{3}{8}"$, filled with carbowax 20 M, 20% on Gas-Chrom P, 60-80 mesh. Helium was the carrier gas at a flow rate of 180 ml per minute. During the early stage of this work, this machine together with the Burrell K-2 was used for the purpose of cross-checking the results obtained.

The temperature of the columns employed for the analytical as well as preparative work depended upon the boiling point of the compounds to be analyzed. When necessary, the temperature was linearly programmed, in order to achieve better resolution. In general, the temperature was increased at a speed of 7.5°C per minute, with the starting temperature, 40°C and the final temperature 200°C .

The quantitative analyses were made by measuring the areas corresponding to the peaks concerned. These areas were compared with the areas obtained using carefully measured amounts of authentic samples.

Infrared spectra were recorded in a Perkin Elmer, Model 221 instrument.

Nuclear magnetic resonance spectra were recorded with a Varian Associates A-60 spectrometer.

Elemental analyses were done by Mrs. Darlene Mahlow at the Chemistry Department of this University.

I. The Dioxanes and Dioxolanes.

A). Commercially available reagents.

The following diols were obtained from Eastman Kodak Co:

1,3-butanediol, 1,3-propanediol, 1,2-propanediol.

B). Preparation of the dioxanes and dioxolanes.

2,2,4-Trimethyl-1,3-dioxane was prepared according to the procedure published by Leggetter, Diner and Brown (41). A mixture of 90 g (1.0 mole) of 1,3-butanediol, anhydrous magnesium sulfate (40 g), p-toluene-sulfonic acid (1 g), and acetone (600 ml), was shaken at room temperature for 60 hours.

The filtrate from this mixture was concentrated and the residue poured into saturated aqueous sodium carbonate. This aqueous material was extracted with ether and the ether extract dried over anhydrous sodium sulfate. The solid was separated and the ether evaporated leaving a

residue which upon fractional distillation gave the required dioxane.

Yield, 40%. B.p., 125°C at 700 mm. η_D^{25} , 1.4190. Lit. b.p., 130-131°C at 758 mm; η_D^{20} , 1.41896 (69).

2-Phenyl-1,3-dioxane was prepared according to published directions (41).

A mixture of benzaldehyde (60 g, 0.57 mole), 1,3-propanediol (38 g, 0.5 mole), *p*-toluenesulfonic acid (1 g) and toluene was heated under reflux in an apparatus equipped with a Dean-Stark water separator (70) until the requisite amount of H₂O (9 ml) was removed. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate and the organic layer separated, washed with water and dried over anhydrous sulfate. By fractional distillation the required 1,3-dioxane was obtained in 60% yield. B.p., 105°C at 3.7 mm. When cooled, the liquid solidified, and after crystallization from Skellysolve B, melted at 45-46°C. Lit. m.p., 45-46°C; b.p., 95-96°C at 1.2 mm (41).

2-Methyl-1,3-dioxane was prepared according to Hibbert and Timm (71).

A mixture of 38 g (0.5 mole) of 1,3-propanediol and 22 g of paraldehyde (0.5 mole of acetaldehyde) was placed in a flask provided with a good condenser. To this was added 0.25 g of 40% aqueous sulfuric acid, and the mixture then kept at 100°C for 10 hours. Two layers were formed. The upper layer with the acetal and some unreacted aldehyde was separated, and the lower layer was neutralized with sodium carbonate and extracted with ether. The ether extract was combined with the upper layer, and the solution dried over anhydrous sodium carbonate. The solid was separated

and the ether removed from the filtrate. The residual liquid was fractionally distilled and the expected 1,3-dioxane obtained in 45% yield. B. p. , 110°C at 710 mm; η_D^{25} , 1.4106. Lit. b.p. , 110°C; η_D^{28} , 1.4102 (71).

4-Methyl-1,3-dioxane was prepared according to the directions published by Carlin and Smith (72). A stirred mixture of 250 g (2.8 mole) of 1,3-butanediol, 87 g of paraformaldehyde (2.9 moles of formaldehyde) and 5 ml of concentrated sulfuric acid was heated so that most of the liquid was removed by distillation. The dark residue was poured onto an ice salt mixture and the upper layer was washed with aqueous sodium bicarbonate, separated and distilled. This distillate was combined with the previous distillate. The aqueous layer of the combined distillates was saturated with sodium chloride, and the organic layer containing the 4-methyl-1,3-dioxane was separated, dried over potassium hydroxide and fractionally distilled affording 180 g (47%) of the expected 1,3-dioxane. B.p. , 110°C at 695 mm; η_D^{23} , 1.4161. Lit. b.p. , 113°C at 740 mm; η_D^{20} , 1.4160 (72).

4-Methyl-1,3-dioxolane was prepared according to Leggetter and Brown (1). A mixture of paraformaldehyde (33 g, 1.1 moles), 1,2-propanediol (76 g, 1.0 mole), anhydrous magnesium sulfate (30 g) and concentrated hydrochloric acid (2 ml) was refluxed for 5 hours. The reaction mixture was cooled and filtered. The filtrate was neutralized with sodium bicarbonate, then dried over anhydrous magnesium sulfate and fractionally distilled to give 55 g (65%) of the 1,3-dioxolane. B.p. , 80°C at 695 mm; η_D^{25} , 1.3983. Lit. b.p. , 82-83°C at 700 mm (1), 88-89°C at 755 mm (73);

η_D^{25} , 1.3983. Lit. b.p., 82-83°C at 700 mm (1), 88-89°C at 755 mm (73);
 η_D^{20} , 1.3989 (26).

Using the same procedure employed for the preparation of 2-methyl-1,3-dioxane, the following compounds were prepared:

2-Methyl-1,3-dioxolane, from ethylene glycol and acetaldehyde. Yield, 40%.
 B.p., 76°C at 700 mm; η_D^{25} , 1.3968. Lit. b.p., 81°C at 767 mm; η_D^{20} , 1.3972 (26).

2,2,4-Trimethyl-1,3-dioxolane from acetone and 1,2-propanediol. Yield 30%.
 B.p., 95°C at 700 mm; η_D^{25} , 1.3944. Lit. b.p., 99-100°C at 761 mm; η_D^{20} , 1.3946 (26).

2-Phenyl-1,3-dioxolane from benzaldehyde and ethylene glycol. Yield 52%.
 B.p., 114-116°C at 20 mm; η_D^{25} , 1.5266. Lit. b.p., 109°C at 14 mm; η_D^{20} , 1.5267 (25).

II. The Tetrahydropyranyl Ethers.

A). Commercially available reagents.

4,5-Dihydropyran and ethyl vinyl ether were obtained from Eastman Kodak Co..

Phenol, 2,6-dichlorophenol, p-methylphenol, 3,4,-dimethylphenol, and p-t-butylphenol were obtained from Aldrich Chemical Co.

Methyl vinyl ketone was obtained from Matheson, Coleman and Bell.

6-Hydroxymethyl-4,5-dihydropyran was obtained as a gift from Shell Chemical Co. of Canada, Limited.

Sodium hydride was obtained from Metal Hydrides Corporation.

m-Chloroperoxybenzoic acid was obtained from F.M.C. Corporation
 500 Roosevelt Ave., Cartaret, New Jersey.

B). Preparation of the tetrahydropyranyl ethers.

2-Methoxytetrahydropyran was prepared according to the general instructions given by Woods and Kramer (36). A mixture of 4,5-Dihydropyran (20 g, 0.238 mole) and 200 ml of methanol (previously dried over magnesium turnings) was placed in a flask provided with a reflux condenser and a magnetic stirrer. A drop of concentrated hydrochloric acid was added, whereupon heat was evolved, causing a slight rise in the temperature of the reaction mixture. This stirred mixture was kept at 50°C overnight. A pellet of sodium hydroxide was then added and the bulk of the solvent removed by distillation. The residual liquid was purified by fractional distillation, giving 20.6 g (75%) of the required tetrahydropyran. B.p. 115-118°C at 700 mm; η_D^{23} , 1.4261. Lit b.p., 125°C; η_D , 1.4260 (36).

Using the procedure just mentioned, the following compounds were synthesized.

2-Ethoxytetrahydropyran from anhydrous ethanol and 4,5-dihydropyran.

Yield, 60%. B.p., 132-136°C at 700 mm; η_D^{25} , 1.4223. Lit. b.p., 146°C; η_D , 1.4248 (36).

2-Isopropoxytetrahydropyran from isopropyl alcohol and 4,5-dihydropyran.

Yield, 60%. B.p., 146-148°C at 710 mm; η_D^{25} , 1.4252. Lit. b.p., 154°C at 745 mm (27), 43°C at 10 mm (74), η_D^{20} , 1.4256 (27).

2-t-Butoxytetrahydropyran from t-butyl alcohol and 4,5-dihydropyran.

Yield, 58%. B.p., 52°C at 8 mm; η_D^{25} , 1.4270. Lit. b.p., 54°C at 10 mm (27); η_D^{25} , 1.4268 (75).

2-n-Butoxytetrahydropyran from n-butyl alcohol and 4,5-dihydropyran.

Yield, 55%. B.p., 70°C at 12 mm; η_D^{25} , 1.4293. Lit. b.p., 70-72°C at 11 mm (27); η_D^{25} , 1.4294 (76).

2-n-Hexoxytetrahydropyran from n-hexyl alcohol and 4,5-dihydropyran

yield, 65%. B.p., 110°C at 4.2 mm; η_D^{25} , 1.4338. Lit b.p., 94°C at 3 mm; η_D^{20} , 1.4397 (27).

2-Phenoxytetrahydropyran was prepared following the directions of Woods

and Kramer (36) modified as follows. Equimolar quantities of 4,5-dihydropyran and phenol were mixed and a drop of concentrated hydrochloric acid added. The reaction mixture stood overnight. Ether was then added and the ethereal solution washed several times with a 3N aqueous sodium hydroxide and then dried with anhydrous sodium sulfate. The ether was removed from the filtrate and the residual liquid fractionally distilled. The required product was obtained in 40% yield. B.p., 97°C at 3.75 mm; η_D^{25} , 1.5190. Lit. b.p., 103°C at 4 mm; η_D^{20} , 1.5290 (36).

Using the same procedure the preparation of the 2-phenoxytetrahydropyran above, the following compounds were synthesized.

2-(2,6-Dichlorophenoxy) tetrahydropyran from 2,6-dichlorophenol and

4,5-dihydropyran,, but with the following modification. The residual liquid (15 g) obtained from the dried ether solution was dissolved in a minimum amount of benzene and passed through a column (40 mm, internal diameter) of neutral alumina (250 g) using benzene as eluent. The product

was collected after 250 ml of benzene were passed through the column.

The benzene was evaporated and the residual liquid distilled to give the required product in 45% yield. B.p. , 95-100°C at 0.5 mm; η_D^{25} , 1.5470.

Anal. Calcd. for $C_{11}H_{12}O_2Cl_2$: C , 53.46; H, 4.80; Cl, 28.7.

Found: C , 53.83; H, 5.21; Cl. 28.80.

2-(3,4-Dimethylphenoxy)tetrahydropyran from 3,4-dimethylphenol and

4,5-dihydropyran. Yield, 70%. B.p. , 98-100°C at 1.2 mm; η_D^{25} , 1.5162. Anal. Calcd. for $C_{13}H_{18}O_2$: C , 75.69; H, 8.794.

Found: C , 75.83; H, 9.22.

2-(4-Methylphenoxy)tetrahydropyran from p-methylphenol and 4,5-dihydro-
pyran. Yield, 75%. B.p. , 70°C at 0.3 mm; η_D^{25} , 1.5171. Anal.

Calcd. for $C_{12}H_{16}O_2$: C , 74.96; H, 8.39. Found: C, 74.58; H, 8.36.

2-(4-t-Butylphenoxy)tetrahydropyran from p-t-butylphenol and 4,5-dihydro-
pyran. Yield, 65%. B.p. , 115°C at 1.25 mm; η_D^{25} , 1.5096. Anal.

Calcd. for $C_{15}H_{22}O_2$: C , 76.88; H, 9.46. Found: C , 76.56; H, 9.13.

3-Bromo-2-ethoxytetrahydropyran was prepared according to the procedure employed by Sweet and Brown (55). In a two liter three-necked, round bottomed flask, equipped with a dry ice condenser, efficient stirrer and a 250 ml dropping funnel, was placed 1 l of methanol. This was cooled to -40°C using a dry ice-acetone bath. To this was added 50 ml of liquified ammonia, followed by 90 g of 4,5-dihydropyran. The contents of the flask was kept at -20°C, while a solution of one mole of bromine (160 g) in 100 ml of carbon tetrachloride was added dropwise at a rate of about 2 drops

a second. When the bromine addition was completed the cooling bath was removed and the reaction mixture left overnight at room temperature. The bulk of the solvent was removed in a rotary evaporator and ether was added to the residue until no more ammonium bromide precipitated. The ammonium bromide was removed by filtration and washed with some ether. The combined ethereal washings and filtrate was washed two times with water, then dried over sodium sulfate and finally freed from the solvent. The residue was fractionally distilled, giving pure 2-ethoxy-3-bromotetrahydropyran in 60% yield, as a cis-trans isomeric mixture with a cis/trans ratio of 35/65 (55). B.p., (of the isomeric mixture) 94°C at 18 mm; η_D^{25} , 1.4755. Lit. b.p., 94-96°C at 18 mm; η_D^{25} , 1.4722 (77). The cis and trans isomers were not separated in this work.

6-Ethoxy-2-methyl-4,5-dihydropyran was prepared following the procedure of Longley et al (35), with the following modification. A mixture of 35 g of ethyl vinyl ether, 23.3 g of methyl vinyl ketone and 500 mg of hydroquinone was heated in a bomb at 150°C for 5 hours. Then, the liquid was fractionally distilled under vacuum and 30 g (43%) of the expected product was obtained. B.p., 54°C at 14 mm; η_D^{25} , 1.4393. Lit. b.p., 51°C at 14 mm; η_D^{25} , 1.4393 (35).

2-Ethoxy-6-methyltetrahydropyran was made as follows. The 6-ethoxy-2-methyl-4,5-dihydropyran (52 g, 0.36 mole) in 50 ml of absolute ethanol, containing freshly made Raney nickel (78) was reduced at room temperature over a 24 hour period in a bomb with hydrogen at 1000 pounds per square inch.

The Raney nickel was separated and the alcohol removed from the filtrate by distillation at atmospheric pressure. When the ethanol no longer came over, an analysis of the residual liquid by gas liquid chromatography showed the presence of ethanol to the extent of 20%. Some calcium chloride was then added, and after several hours, a second analysis by gas-liquid chromatograph showed that the alcoholic content had decreased to 10%. The liquid was then filtrated and fractionally distilled, giving 40 g (77%) of product boiling at 84°C at 75 mm. η_{D}^{25} , 1.4220. Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 66.62; H, 11.18. Found: C, 66.71; H, 11.01.

6-Methoxymethyl-4,5-dihydropyran was prepared according to the procedure advocated by Diner, Sweet and Brown (40). To a solution of 6-hydroxymethyl-4,5-dihydropyran (68.4 g, 0.6 mole) and methyl iodide (99.5 g, 0.7 mole) in 350 ml of 1,2-dimethoxyethane (previously dried and distilled from LiAlH_4), all contained in a 1l, three-necked flask, equipped with a condenser, dropping funnel, drying tube and a magnetic stirrer, was added in small portions, 15.6 g (0.65 mole) of sodium hydride, previously washed with dry ethyl ether. This addition was done over a period of 30 minutes. Vigorous hydrogen evolution took place after addition of each of the small portions of the hydride. Heat was evolved and sodium iodide precipitated. A few minutes after the addition of the hydride was completed a further quantity of 10 ml of methyl iodide was added and the solution left at room temperature for one hour. Then, the 1,2-dimethoxyethane and excess methyl iodide were removed by fractional

distillation at atmospheric pressure until the volume was reduced to about one-third.

Anhydrous ether (60 ml) was added, whereupon more sodium iodide precipitated. The mixture was filtered, the sodium iodide washed with ether (20 ml) and the combined washings and filtrate was fractionally distilled at atmospheric pressure. Seventy grams (91%) of product was obtained by fractional distillation of the residual liquid. B.p., 83°C at 65 mm; η_D^{25} , 1.4400. Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.30.

2-Methoxy-6-methoxymethyltetrahydropyran was prepared as follows.

To 10 g (0.08 mole) of 6-methoxymethyl-4,5-dihydropyran dissolved in 250 ml of anhydrous methanol, was added one drop of concentrated hydrochloric acid. The reaction mixture was left for four hours at room temperature. One pellet of sodium hydroxide was then added and most of the methanol was removed by fractional distillation at atmospheric pressure. The residue was then fractionally distilled giving 8 g (62.5%) of product. B.p., 110°C at 75 mm; η_D^{25} , 1.4320. Gas liquid chromatography showed the product to be a mixture of cis and trans isomers in a ratio of 30% to 70%, a result supported by n.m.r. analysis. These isomers were separated by preparative gas liquid chromatography. The corresponding n.m.r. spectra can be seen in pages 59 and 60. Starting with 8 g of the isomeric mixture (boiling at 110°C/75 mm), 2.98 g of the trans isomer and 600 mg of the cis isomer were collected.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07.

Found, for the isomeric mixture: C, 60.07; H, 10.06.

Found, for the trans isomer: C, 60.04; H, 10.35.

Found, for the cis isomer: C, 60.04; H, 9.71.

3-Hydroxy-2-methoxytetrahydropyran was prepared following the directions given by Sweet and Brown (39). 4,5-Dihydropyran (21 g, 0.25 mole) was dissolved in 300 ml of dry methanol contained in a 1 l, three-neck flask equipped with condenser, magnetic stirrer and a low temperature thermometer. The flask and contents were kept between -5°C and -10°C with a dry ice-acetone bath, while 34.4 g (0.2 mole) of m-chloroperoxybenzoic acid was added in small portions over a period of approximately 0.5 hour. The cooling bath was then removed and the reaction mixture stood overnight at room temperature. The solution was then freed from solvent in a rotatory evaporator, and the residual solid suspended in 300 ml of chloroform. The suspension was left in the refrigerator at -20°C for about 1 hour, the precipitated m-chlorobenzoic acid removed, and the chloroform filtrate containing the product was washed with 100 ml of saturated aqueous sodium bicarbonate. The aqueous solution was then extracted once with 100 ml of chloroform and the combined chloroform extracts dried and freed from solvent in a rotary evaporator. The residual liquid was then fractionally distilled affording 20 g (76%) of the desired product. B.p., 56°C at 2 mm; η_D^{25} , 1.4547. Lit. b.p., 56°C at 2 mm; η_D^{23} , 1.4548 (39).

The following compounds were prepared following the same procedure as explained for the preparation of the compound above.

2-Ethoxy-3-hydroxytetrahydropyran from 4,5-dihydropyran and ethanol.

Yield, 70%. B.p., 60°C at 2.2 mm; η_D^{25} , 1.4506. Lit. b.p., 63°C at 2.5 mm; η_D^{25} , 1.4506 (39).

3-Hydroxy-2-isopropoxytetrahydropyran from 4,5-dihydropyran and

isopropyl alcohol. Yield, 70%. B.p., 63°C at 2 mm; η_D^{25} , 1.4469. Lit. b.p., 63°C at 2 mm; η_D^{25} , 1.4467 (39).

The following compounds were prepared using the same procedure as used for the methylation of the 6-hydroxymethyl-4,5-dihydropyran.

2,3-dimethoxytetrahydropyran from 3-hydroxy-2-methoxytetrahydropyran.

Yield, 80%. B.p., 110°C at 110 mm; η_D^{25} , 1.4318. Lit. b.p., 110-111°C at 110 mm; η_D^{25} , 1.4318 (39).

2-Ethoxy-3-methoxytetrahydropyran from 2-ethoxy-3-hydroxytetrahydro-

pyran. Yield, 80%. B.p., 46°C at 5 mm; η_D^{25} , 1.4322. Lit. b.p., 46°C at 5.2 mm; η_D^{25} , 1.4322 (39).

2-Isopropoxy-3-methoxytetrahydropyran from 3-hydroxy-2-isopropoxytetra-

hydropyran. Yield, 78%. B.p., 93°C at 30 mm; η_D^{25} , 1.4299. Lit. b.p., 93°C at 30 mm; η_D^{25} , 1.4299 (39).

6-Methyl-4,5-dihydropyran was prepared by standard literature procedure

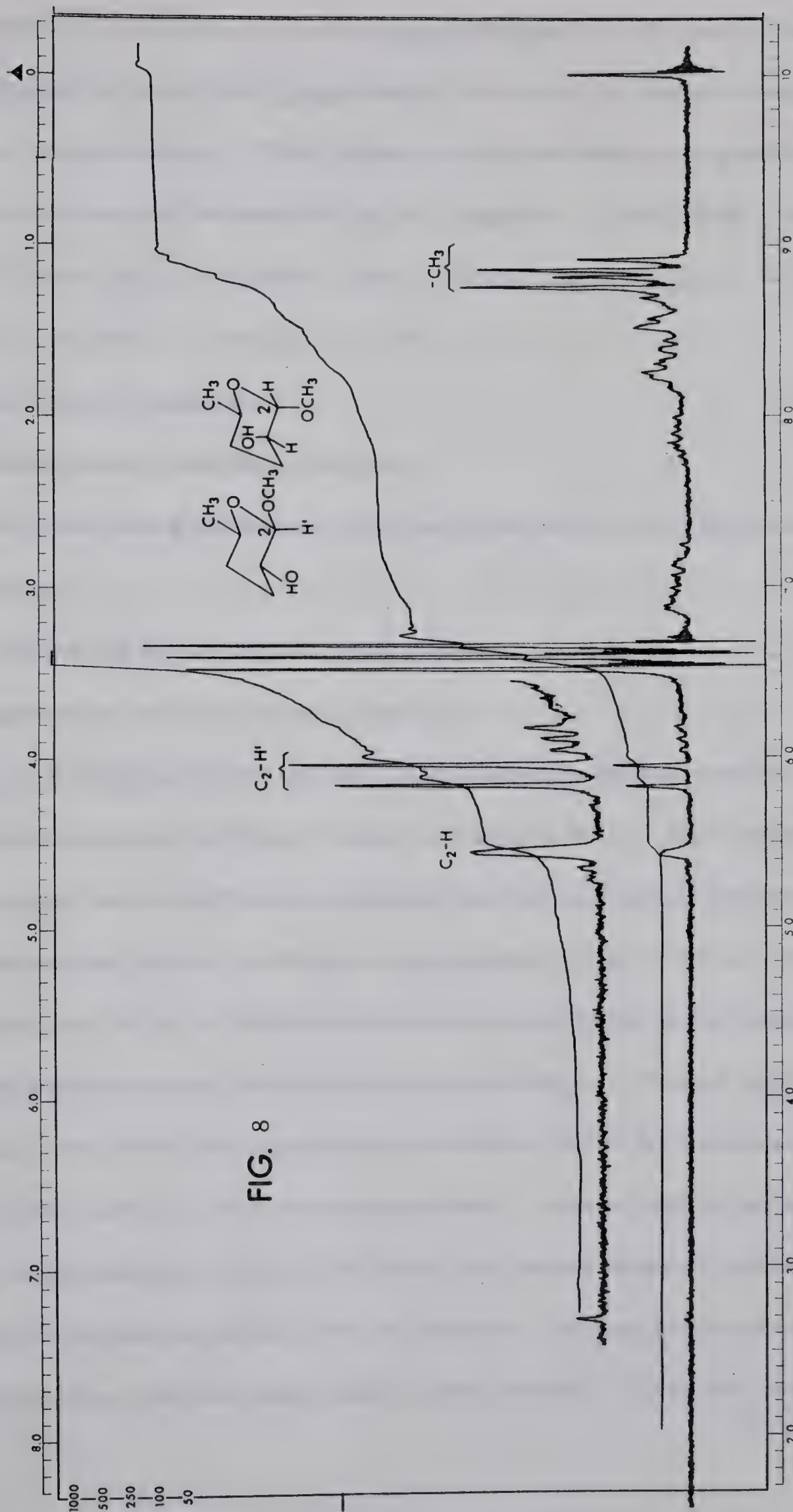
(79) involving the lithium aluminum hydride reduction of the tosyl derivative of the 6-hydroxymethyl-4,5-dihydropyran. This tosyl derivative was prepared by dissolving the 6-hydroxymethyl-4,5-dihydropyran in pyridine,

adding one equivalent of p-toluenesulfonyl chloride and allowing this solution to stand at 0°C overnight. The reaction mixture was then poured into water, the aqueous mixture extracted with ether, the ether solution washed with water several times, then dried and freed from solvent in a rotary evaporator. The residual liquid was then treated with lithium aluminum hydride. The description of this method is given as an example of other reductions with the same reagent in this thesis. The crude 6-p-toluenesulfonyloxymethyl-4,5-dihydropyran (10 g, 0.04 mole), dissolved in 50 ml of dry ethyl ether, was added dropwise to a cooled (0°C) stirred suspension of lithium aluminum hydride (3.8 g, 0.1 mole) in 100 ml of anhydrous ether. After complete addition of the reagents, the reaction mixture was stirred for one hour at room temperature. The hydride was then destroyed by first cooling the mixture to -5°C (using a bath of acetone containing some dry ice) and then adding dropwise to this, 4 ml of water followed by 4 ml of 15% aqueous sodium hydroxide, and finally 4 ml of water. After removal of the inorganic solid by filtration, the ether solution was dried over anhydrous magnesium sulfate. Removal of the ether afforded an oil which was purified by fractional distillation to give the required product in 25% overall yield. B.p., 70-72°C at 700 mm; η_D^{25} , 1.4311. Lit. b.p., 76-80°C at 737 mm; η_D^{25} , 1.4314 (80).

3-Hydroxy-2-methoxy-6-methyltetrahydropyran was prepared following the general procedure advocated by Sweet and Brown (39). To a cold (-5°C) solution of 0.1 mole (9.8 g) of 6-methyl-4,5-dihydropyran in 300 ml of

anhydrous methanol, was added over a period of half an hour, with stirring, 0.1 mole (17.2 g) of m-chloroperoxybenzoic acid, in the form of a suspension in 100 ml of chloroform. The temperature during the addition was kept at -5°C . The stirring was continued for about half an hour after the addition. The cooling bath was then removed, the stirring interrupted, and the clear, homogenous reaction mixture was left overnight at room temperature. The solvents were then removed under reduced pressure in a rotary evaporator, with the water bath at 50°C . The residue consisting of a mixture of m-chlorobenzoic acid and 3-hydroxy-2-methoxy-6-methyl-tetrahydropyran was shaken with 300 ml of chloroform and then the mixture cooled to 0°C and filtered under suction. The cake of m-chlorobenzoic acid was washed twice with 20 ml portions of cold chloroform. The combined chloroform solutions were washed with saturated aqueous sodium bicarbonate, and the aqueous sodium bicarbonate layer extracted once with 50 ml of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered and evaporated in the rotary evaporator. The residue (8 g) was then distilled affording 7 g (61.5%) of the expected product. B.p., 65°C at 4.5 mm; η_{D}^{25} , 1.4473. Anal. Calcd. for $\text{C}_7\text{H}_{14}\text{O}_3$: C, 57.51; H, 9.65. Found: C, 57.80; H, 9.37. The n.m.r. spectrum of this compound can be seen in Fig. 8 page 149.

2,3-Dimethoxy-6-methyltetrahydropyran was obtained from methylation of the above product by the procedure used to methylate the 6-hydroxymethyl-4,5-dihydropyran above. The product was a mixture of the two possible



N.m.r. spectrum of the cis,trans-3-hydroxy-2-methoxy-6-methyltetrahydropyran.

trans isomers, in a ratio of 2 of the trans diequatorial (considering the alkoxy groups) to one of the trans diaxial, as shown by nuclear magnetic resonance spectroscopy. This isomeric mixture was not separated. The n.m.r. spectrum can be seen in Fig. 6, page 86. Yield, 82%. B.p., 87°C at 23 mm; η_{D}^{25} , 1.4284. Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_3$: C, 59.98; H, 10.07. Found: C, 60.31; H, 9.92.

III. The Glucopyranosides

A). Commercially available reagents.

2-Deoxy- α -D-glucose was obtained from Nutritional Biochemicals Corporation.

D-sorbitol was obtained from Fisher Scientific Co.

B). Preparation of the glucopyranosides

Methyl 2,3,4,6-tetra-O-methyl- α -D-glucopyranoside was prepared by the method described by Diner, Sweet and Brown (40). Into a three-necked flask equipped with an efficient condenser and a mechanical stirrer was placed anhydrous methyl α -D-glucopyranoside (9.7 g, 0.05 mole) dissolved in a mixture of 130 ml of dimethylformamide and 70 ml of 1,2-dimethoxyethane (previously dried and distilled from LiAlH_4). Methyl iodide (32.5 g, 0.23 mole) was added and the solution cooled to -10°C by immersion of the flask for a time in a dry ice-acetone bath. About half of the sodium hydride (total amount, 4.8 g, 0.02 mole) was added in small portions over a period of 7-8 minutes to the stirred solution. A gentle evolution of gas occurred and the reaction temperature rose slowly. Then the rest of the

hydride was added all at once. When the temperature reached 30°C , the reaction became vigorous, whereupon the flask was immersed in the dry ice-acetone bath. A maximum temperature of 60°C was reached and maintained for about 5 min. and then the temperature dropped rapidly. The cooling bath was removed, and the mixture was stirred for a time (total reaction time ~ 1 h) and finally poured cautiously into 600 ml of water containing 100 g of dissolved sodium chloride. The resulting mixture was extracted with chloroform (5 x 100 ml). The combined extracts were dried (Na_2SO_4) and freed from solvents by rotary evaporation and finally by distillation under vacuum at 2 mm with a bath temperature of 70°C . The crude residue (11.5 g, 92%), when analyzed by gas liquid chromatography, consisted of only two substances, dimethyl formamide ($\sim 4\%$ on a molar basis) and the fully methylated glucoside. Removal of the dimethyl formamide was accomplished by passage of the crude product through a column of Woelm neutral alumina (150 g), using successively the eluents (200 ml of each) benzene-pentane (7:4), benzene-chloroform (1:1), and benzene-chloroform (1:3). The sequence of increasing polarity of eluents was used to avoid the possibility of elution of the contaminating dimethyl formamide. The higher polarity was required to remove the last portion of the pentamethyl glucoside from the strongly adsorbing column. When British Drug Houses alumina was used, the eluent, benzene-pentane (7:4) was sufficient to remove selectively all of the glucoside. The resulting pure methyl 2,3,4,6-tetra-O-methyl- α -D-glucoside (10.5 g, 84%)

was identical in all respects with an authentic sample (81, 82). The infra-red spectrum (neat) showed no absorption in the $3600-3300\text{ cm}^{-1}$ region (-OH). Methyl 2-deoxy- α -D-glucopyranoside was prepared by dissolving 2-deoxy- α -D-glucose (5 g) in 200 ml of a solution of 5% gaseous hydrogen chloride in methanol. This solution was kept at 40°C for 40 min., whereupon enough silver carbonate was added to neutralize the acid. The liquid was filtered and the methanol evaporated from the filtrate in a rotary evaporator. The syrup crystallized when left for two days. Yield, 45%. M.p., $91-92^{\circ}\text{C}$. Lit. m.p., $91-92^{\circ}\text{C}$ (83).

Methyl 2-deoxy-3,4,6-tri-O-methyl- α -D-glucopyranoside* was prepared following the same method used for the methylation of the methyl α -D-glucopyranoside, but starting with methyl 2-deoxy- α -D-glucopyranoside. Yield, 80%. η_{D}^{25} , 1.4385.

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{O}_5$: C, 54.53; H, 9.15.

Found: C, 54.68; H, 9.09.

IV.. Preparation of the Products Obtained by Hydrogenolysis of the Glucopyranosides and Cyclic Acetals and Ketals.

A). Commercially available reagents.

2-Ethoxyethanol was obtained from Eastman Kodak Co..

B). Preparation of the products.

1,5-Anhydro-2,3,4,6-tetra-O-methyl-D-glucitol was prepared by methylation of 1,5-anhydro-D-glucitol using the same technique as explained for

*The same substance was obtained by methylation with the silver oxide-methyl iodide method used by J. Purdie and J. C. Irvine, J. Chem. Soc. 83, 1021 (1903).

the methylation of methyl α -D-glucopyranoside. The crude product was purified by chromatography on a column of neutral alumina (Woelm) using 100 g of alumina for each 10 g of product, and using as eluent a mixture of benzene-pentane (7/4, v/v). Yield, 60%. B.p., 78°C at 2 mm; η_D^{25} , 1.4438. Lit. b.p., 80°C at 2 mm; η_D^{22} , 1.4444 (84). The same substance was obtained by methylation using the methyl sulfate-barium oxide (hydroxide) method (85).

This latter method is given as an illustration.

In a 1 l flask provided with, an efficient stirrer and dropping funnel are placed 28.6 g (0.175 mole) of 1,5-anhydro-D-glucitol, 33 g (0.21 equivalent) of $\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$ and 33 g of barium oxide. To this was added 200 ml of a mixture of dimethylformamide and dimethylsulfoxide (50/50, v/v). To the mixture, cooled in an ice-water bath, was added dropwise 22 g of dimethyl sulfate. When the addition was finished, the cooling bath was removed and the reaction mixture left overnight under constant stirring. Then 20 ml of concentrated ammonia was added, followed by 500 ml of water. The mixture was then extracted several times with ether, the ether extract dried over anhydrous sodium sulfate. The ether was removed in a rotary evaporator, and the crude product purified as described for the preparation immediately above. Yield, 25%.

The precursor 1,5-anhydro-D-glucitol was prepared by reduction of the previously prepared acetobromoglucose (86) with LiAlH_4 using the standard technique (79). The crude yellow syrup without further purification

was methylated as explained immediately above .

Hexamethylsorbitol was prepared by methylation of sorbitol by the method just described immediately above. Yield, 32%. B.p. , 98°C at 1.5 mm; η_D^{25} , 1.4317. Lit. b.p. , 100°C at 1.5 mm; η_D^{22} , 1.4367 (84).

3-Benzyloxy-1-propanol was made following the directions given by Leggetter, Diner and Brown (40). Sodium metal (2.7 g, 0.12 mole) was added slowly to 30 ml of hot 1,3-propanediol. To the resulting solution was added slowly 15 g (0.12 mole) of benzyl chloride. The mixture was heated at 120°C for 2 hours , then cooled and poured into water. The aqueous solution was extracted with ether , the dried (MgSO₄) ether extract was freed from solvent and the residue fractionally distilled giving 7.2 g (37%) of the alcohol. B.p. , 107°C at 1.5 mm; η_D^{25} , 1.5122. Lit. b.p. , 155°C at 23 mm; η_D^{20} , 1.5128 (87).

2-Benzyloxyethanol was prepared according to the method advocated by Leggetter and Brown (1). The procedure is the same as the one used for the preparation of the 3-benzyloxy-1-propanol above , using 1,2-ethanediol instead of 1,3-propanediol. Yield, 40%. B.p. , 114-116°C at 6 mm; η_D^{25} , 1.5236. Lit. b.p. , 116°C at 6 mm (1). η_D^{20} , 1.5233 (88).

3-Ethoxy-1-propanol was synthesized following Leggetter , Diner and Brown's method (40). Sodium (5 g, 0.22 mole) was dissolved in a mixture of 120 ml of ethyl alcohol and 50 ml of dry xylene , and the resulting solution was stirred keeping it at 100°C , while 3-chloro-1-propanol (19.0 g, 0.2 mole) was added dropwise. The mixture was then stirred for 3 h , cooled and poured

into cold water. The ether extract was dried over anhydrous magnesium sulfate, freed from solvents and fractionally distilled. Yield, 32%. B.p., 150°C at 700 mm; n_D^{25} , 1.4151. Lit. b.p., 157°C (89); n_D^{25} , 1.4169 (90).

1-Methoxy-2-propanol was prepared following the general method advocated by Chitwood and Freure (91). 1,2-Epoxypropane (15.0 g, 0.26 mole) was added dropwise to a solution of 14 g of commercial sodium methoxide in 100 ml of dry methanol, kept cool by immersion of the flask in an ice-water bath. The solution was left overnight at room temperature, and then poured into cold water. The aqueous mixture was extracted with ether, the ether solution dried over magnesium sulfate, and then freed from the ether. The residual liquid was distilled, and 15 g (65%) of the expected product obtained. B.p., 113-116°C at 700 mm; n_D^{25} , 1.4014. Lit. b.p., 115-116°C at 700 mm (1); n_D^{25} , 1.4017 (92).

2-Methoxy-1-propanol was prepared according to Leggetter and Brown (1) by reduction with lithium aluminum hydride of the methyl α -methoxypropionate using the standard technique (79). Yield, 65%. B.p., 123-126°C at 700 mm; n_D^{25} , 1.4048. Lit. b.p., 125°C at 700 mm (1); n_D^{25} , 1.4048 (92).

The methyl α -methoxypropionate prepared in this laboratory by B. E. Leggetter (1) was used for the above preparation.

3-Methoxy-1-butanol was prepared most conveniently by reduction with $\text{LiAlH}_4/\text{AlCl}_3$ of 4-methyl-1,3-dioxane. The details of this type of reduction can be seen in page 168 below. The physical properties of the

product were identical to those reported in the literature. Yield, 62%.

B.p. , 156-157°C at 700 mm; η_D^{25} , 1.4146. Lit. b.p. , 159-160°C; η_D^{25} , 1.4148 (93).

4-Methoxy-2-butanol was prepared according to the method employed by Leggetter , Diner and Brown (40). This method was used above for the synthesis of 3-benzyloxy-1-propanol. The starting materials were 1,3-butanediol and methyl iodide. Yield, 42%. B.p. , 85°C at 60 mm; η_D^{25} , 1.4146. Lit. b.p. , 85°C at 62 mm (1); η_D^{20} , 1.4143 (94).

4-Isopropoxy-2-butanol was prepared by the same procedure used for the above synthesis of 4-methoxy-2-butanol (40) starting with 1,3-butanediol and 2-bromopropane. Yield, 35%. B.p. , 94°C at 45 mm. η_D^{25} , 1.4518. Lit. b.p. , 94°C at 45 mm; η_D^{25} , 1.4518 (40).

The following compounds were obtained from B. E. Leggetter:

1-Isopropoxy-2-propanol , 2-Isopropoxy-1-propanol , and 3-Isopropoxy-1-butanol (95).

V. Preparation of the Reduction Products From the Hydrogenolysis of the Tetrahydropyranyl Ethers.

A). Commercially available reagents.

1,5-Pentanediol and ethyl vinyl ether were obtained from Eastman Kodak Co..

4-Penten-1-ol was obtained from City Chemical Co..

5-Hexen-2-one was obtained from Matheson , Coleman and Bell.

B). Preparation of the products and precursors.

Acetaldehyde ethyl 4-pentenyl acetal. A mixture of 8.6 g (0.1 mole) of 4-penten-1-ol, 100 ml of ethyl vinyl ether and a drop of concentrated hydrochloric acid in a 500 ml flask provided with a condenser was left at room temperature for two hours. The addition of the acid resulted in an initial temperature rise of 15°C. This dropped, soon after, to about room temperature. A pellet of sodium hydroxide was then added and the excess ethyl vinyl ether was removed in a rotary evaporator under vacuum. The residue was then fractionally distilled providing 14 g (88%) of the acetal. B. p., 90°C at 42 mm; n_D^{25} , 1.4135.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47.

Found: C, 68.33; H, 11.18.

Acetaldehyde 4,5-epoxypentyl ethyl acetal. A solution of 13 g (0.082 mole) of acetaldehyde ethyl 4-pentenyl acetal in 200 ml of chloroform was cooled to 0°C. To this stirred solution, was added m-chloroperoxybenzoic acid (10.5 g, 0.08 mole) in small portions over a period of 0.5 h. When the addition was finished, the cooling bath was removed and the solution stood overnight at room temperature. Then the solution was cooled to about 0°C, whereupon m-chlorobenzoic acid precipitated. The precipitate was removed by filtration and washed with cold chloroform (2 x 20 ml). The combined washings and filtrate was washed several times with 10% aqueous sodium carbonate. The combined aqueous sodium carbonate solutions were then saturated with sodium chloride and extracted with 100 ml

of chloroform. The chloroform solutions were then combined, dried over magnesium sulfate and finally freed from solvent in a rotary evaporator.

The residue was distilled, giving 11 g (77%) of the product. B.p., 60°C at 0.5 mm; n_D^{25} , 1.4227. Anal. Calcd. for $C_9H_{18}O_7$: C, 62.04; H, 10.41. Found: C, 61.84; H, 10.38.

Acetaldehyde ethyl 5-ethoxy-4-hydroxypentyl acetal. Acetaldehyde 4,5-

epoxypentyl ethyl acetal (10 g, 0.057 mole) was dissolved in 100 ml of a solution of sodium ethoxide in ethanol previously prepared by adding 1.4 g (0.058 mole) of sodium hydride to absolute ethanol. The reaction mixture was kept at 60°C for 2 hours and then left overnight at room temperature.

The mixture was first neutralized carefully with concentrated hydrochloric acid using phenolphthalein as internal indicator, and then reduced to one-third of its volume in a rotary evaporator under vacuum. Ether was then added, until sodium chloride no longer precipitated. The salt was removed by filtration, the filtrate dried over magnesium sulfate and the solvents removed in a rotary evaporator. The residue was then fractionally distilled through a short (5 cm) Vigreux column. Yield, 8.5 g (67.5%). B.p., 90°C at 0.4 mm; n_D^{25} , 1.4320. Anal. Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 59.55; H, 10.66.

Acetaldehyde ethyl 5-ethoxy-4-methoxypentyl acetal was obtained by

methylation of the acetaldehyde ethyl 5-ethoxy-4-hydroxypentyl acetal using the same procedure as explained for the methylation of the 6-hydroxy-methyl-4,5-dihydropyran. Yield, 75%. B.p., 70°C at 0.3 mm;

η_D^{25} , 1.4198. Anal. Calcd. for $C_{12}H_{26}O_4$: C, 61.51; H, 11.18.

Found: C, 61.23; H, 11.25.

5-Ethoxy-4-methoxy-1-pentanol. To 3 g of acetaldehyde ethyl 5-ethoxy-4-methoxypentyl acetal was added 1 ml of water, followed by a few crystals of p-toluenesulfonic acid. The reaction mixture was kept on the steam bath for one hour and then a small amount of anhydrous sodium carbonate was added. After 15 min the liquid was filtered and the filtrate distilled in an apparatus provided with Claisen head and condenser. Yield, 1.46 g (80%). B.p., 57°C at 0.4 mm; η_D^{25} , 1.4316.

Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.57; H, 10.93.

5-Ethoxy-1,4-pentanediol was obtained by hydrolysis of acetaldehyde ethyl 5-ethoxy-4-hydroxypentyl acetal as described immediately above. Yield, 75%. B.p., 67°C at 0.3 mm; η_D^{25} , 1.4500.

Anal. Calcd. for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.81; H, 10.75.

Acetaldehyde ethyl 4-hydroxy-5-isopropoxypentyl acetal was prepared using the same procedure as explained for the 5-ethoxy derivative above, using sodium isopropoxide instead of sodium ethoxide. Yield, 70%.

B.p., 75°C at 0.3 mm; η_D^{25} , 1.4200.

Anal. Calcd. for $C_{12}H_{26}O_4$: C, 61.51; H, 11.18. Found: C, 61.42; H, 11.07.

Acetaldehyde ethyl 5-isopropoxy-4-methoxypentyl acetal was made by

methylation of the acetaldehyde ethyl 4-hydroxy-5-isopropoxypentyl acetal using the same procedure as explained for the acetaldehyde ethyl 5-ethoxy-4-hydroxypentyl acetal. Yield, 85%. B.p., 65°C at 0.3 mm; η_D^{25} , 1.4210. Anal. Calcd. for $C_{13}H_{28}O_4$: C, 62.87; H, 11.36. Found: C, 62.41; H, 11.07.

5-Isopropoxy-4-methoxy-1-pentanol was made by hydrolysis of the acetaldehyde ethyl 5-isopropoxy-4-methoxypentyl acetal using the same technique as employed for the preparation of the 5-ethoxy-4-methoxy-1-pentanol. Yield, 70%. B.p., 60°C at 0.3 mm; η_D^{25} , 1.4318. Anal. Calcd. for $C_9H_{20}O_3$: C, 61.33; H, 11.44. Found: C, 61.38; H, 11.46.

5-Isopropoxy-1,4-pentanediol was made by hydrolysis of the acetaldehyde ethyl 4-hydroxy-5-isopropoxypentyl acetal as described for the preparation of 5-ethoxy-4-methoxy-1-pentanol. Yield, 70%. B.p., 87°C at 0.6 mm; η_D^{25} , 1.4465. Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.04; H, 10.96.

5-Methoxy-1,4-pentanediol. Acetaldehyde ethyl 4,5-epoxypentyl acetal (10 g, 0.057 mole) was treated at room temperature with 5.4 g (0.1 mole) of commercial sodium methoxide dissolved in 100 ml of dry methanol. The reaction mixture was left for 5 h and then neutralized carefully with concentrated hydrochloric acid using phenolphthalein as internal indicator. The reaction mixture was then freed from two-thirds of the solvent in a rotary evaporator, and then ether was added to the residue until precipitation of sodium chloride was no longer observed. The

sodium chloride was then removed by filtration and the ethereal filtrate dried over magnesium sulfate. Removal of the ether followed by distillation of the residue gave 8 g of a crude product which gas liquid chromatography showed to be ~95% pure. Three grams of this material was then hydrolysed using the technique employed for the preparation of 5-ethoxy-4-methoxy-1-pentanol above, affording 1.2 g (62%) of the expected diol. B.p., 80°C at 0.4 mm; η_D^{25} , 1.4515. Anal. Calcd. for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.44; H, 10.15.

Acetaldehyde ethyl 4,5-dimethoxypentyl acetal. The remainder of the 8 g of crude material* obtained above was methylated using the procedure as described for the preparation of acetaldehyde ethyl 5-ethoxy-4-methoxypentyl acetal. The expected product was obtained by fractional distillation in 85% yield. B.p., 78°C at 0.3 mm; η_D^{25} , 1.4228. Anal. Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 59.98; H, 10.86.

4,5-Dimethoxy-1-pentanol was prepared by hydrolysis of acetaldehyde ethyl 4,5-dimethoxypentyl acetal using the method described for the preparation of 5-ethoxy-4-methoxy-1-pentanol. Yield, 83%. B.p., 65°C at 2.25 mm; η_D^{25} , 1.4340. Anal. Calcd. for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.46; H, 10.65.

ω -Chloro-n-amyl acetate was synthesized according to the instructions given by Cason et al (96). A mixture of 175 g (2.03 moles) of tetrahydropyran (prepared from reduction of 4,5-dihydropyran with hydrogen over Pt

*Acetaldehyde ethyl 4-hydroxy-5-methoxypentyl acetal.

at 30 p.s.i.; b.p., 82°C at 710 mm; lit. b.p., $85^{\circ}\text{C}/760$ mm (97)), 8 g of freshly fused zinc chloride and 159 g (2.03 moles) of acetyl chloride was heated under reflux for two hours. The cooled reaction mixture was filtered and fractionally distilled. The expected ester was collected at $113\text{--}115^{\circ}\text{C}$ at 34 mm in 80% yield (260 g). η_{D}^{25} , 1.4370. Lit. b.p., $109\text{--}112^{\circ}\text{C}$ at 24 mm (96); η_{α}^{20} , 1.43791 (98).

5-Chloro-1-pentanol was prepared by reduction of ω -chloro-n-amyl acetate with lithium aluminum hydride using the standard technique (79). Yield, 82%. B.p., 103°C at 8 mm; η_{D}^{25} , 1.4520. Lit. b.p., 103°C at 8 mm; η_{D}^{20} , 1.4518 (99).

Acetaldehyde ethyl 5-chloropentyl acetal. The 5-chloro-1-pentanol was treated with a 10-fold excess of ethyl vinyl ether and a drop of concentrated hydrochloric acid as catalyst. The reaction mixture was left for 5 h at room temperature. A pellet of sodium hydroxide was added and the solvent removed in a rotary evaporator under vacuum. The residual liquid was fractionally distilled. The product was collected at 50°C at 0.3 mm. Yield, 75%; η_{D}^{25} , 1.4310. Anal. Calcd. for $\text{C}_9\text{H}_{19}\text{O}_2\text{Cl}$: C, 55.51; H, 9.83; Cl, 18.2. Found: C, 55.69; H, 9.46; Cl, 17.9.

5-Methoxy-1-pentanol. Acetaldehyde ethyl 5-chloropentyl acetal (5 g, 0.025 mole), in a solution of 5 g of sodium methoxide in 100 ml of methanol was left overnight under gentle reflux. The cooled solution was neutralized carefully with concentrated hydrochloric acid using phenolphthalein as internal indicator. Ether was added until no more sodium chloride precipitated. The sodium chloride was removed by filtration, and the

ethereal filtrate dried over magnesium sulfate. The ether solution was then freed of solvent in a rotary evaporator, and the residual liquid was hydrolyzed by the same method as used for the preparation of 5-ethoxy-4-methoxy-1-pentanol above. The expected 5-methoxy-1-pentanol was obtained in 20% yield (600 mg) based on the acetaldehyde ethyl 5-chloropentyl acetal. B.p., 60°C at 1.5 mm; η_D^{25} , 1.4235. Anal. Calcd. for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found: C, 60.95; H, 11.17.

Alternative way of preparing 5-methoxy-1-pentanol. A mixture of 52 g (0.5 mole) of 1,5-pentanediol, 500 ml of 1,2-dimethoxyethane (dried over $LiAlH_4$) and 71 g (0.5 mole) of methyl iodide was placed in a 1 l, three-neck flask equipped with condenser and stirrer. Then, 12 g (0.5 mole) of sodium hydride was added in small amounts over a period of 1 h. The reaction mixture was stirred at room temperature for 2 h, then about half of the solvent was removed in a rotary evaporator. Ether was added to the residue until precipitation of sodium iodide was no longer observed. The ether and the rest of the 1,2-dimethoxyethane were removed and the residual liquid fractionally distilled giving a product whose physical properties were identical to those obtained from the product synthesized by the method immediately above. Yield, 40%. B.p., 60°C at 1.5 mm; η_D^{25} , 1.4235.

5-Ethoxy-1-pentanol was prepared by the same procedure employed for the preparation of 5-methoxy-1-pentanol above, starting with acetaldehyde ethyl 5-chloropentyl acetal and sodium ethoxide in ethanol. Yield, 30%.

B.p. , 60°C at 0.5 mm; η_D^{25} , 1.4263. Anal. Calcd. for $C_7H_{16}O_2$:
C, 63.59; H, 12.19. Found: C, 63.49; H, 12.35.

5-Isopropoxy-1-pentanol was made following the same procedure described immediately above, using acetaldehyde ethyl 5-chloropentyl acetal and sodium isopropoxide in isopropyl alcohol. Yield, 35%. B.p. , 57°C at 0.75 mm; η_D^{25} , 1.4276. Lit. b.p. , 98-100°C at 12 mm; η_D^{20} , 1.4313 (27).

The following compounds were prepared by the $LiAlH_4/AlCl_3$ reduction of the corresponding pyranyl ether, as described on page 168.

5-t-Butoxy-1-pentanol, from the reduction of 2-t-butoxytetrahydropyran. Yield, 70%. B.p. , 102°C at 10 mm; η_D^{25} , 1.4344. Lit. b.p. , 106°C at 10 mm; η_D^{20} , 1.4348 (27).

6-Ethoxy-2-hexanol, from the reduction of 6-ethoxy-2-methyl-4,5-dihydropyran. The resulting crude material, showed a strong carbonyl absorption at 6 μ in the infrared spectrum, hence was subjected again to reduction with lithium aluminum hydride. The expected alcohol was produced in 40% yield based on the starting material. B.p. , 53°C at 0.8 mm; η_D^{25} , 1.4290. Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.23; H, 12.71.

5-n-Butoxy-1-pentanol was prepared from reduction of the 2-n-butoxytetrahydropyran. Yield, 38%. B.p. , 118°C at 10 mm; η_D^{25} , 1.4354. Lit. b.p. , 120°C at 10 mm; η_D^{20} , 1.4376 (27).

5-n-Hexoxy-1-pentanol, from reduction of the 2-n-hexoxytetrahydropyran. Yield, 40%. B.p. , 110°C at 4.2 mm; η_D^{25} , 1.4388. Lit. b.p. , 117-118°C

at 8.5 mm; η_D^t not reported (27).

1,6-Dimethoxy-2-hexanol, from reduction of 2-methoxy-6-methoxymethyl-tetrahydropyran. Yield, 60%. B.p., 62-65°C at 0.75 mm; 59°C at 0.3 mm; η_D^{25} , 1.4327. Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.10; H, 10.50.

5-Methoxy-2-methyltetrahydropyran. Sodium hydride (2.4 g, 0.1 mole) and methyl iodide (20 g, 0.14 mole) in 200 ml of 1,2-dimethoxyethane (dried over $LiAlH_4$) were added to a 1 l, three-neck flask, provided with condenser, magnetic stirrer, drying tube and dropping funnel. To this suspension, was added a solution of 11.6 g (0.1 mole) of 1,2-epoxy-5-hydroxyhexane in 200 ml of dry 1,2-dimethoxyethane at the rate of 2 drops per second. One hour after the addition was completed, the stirring was interrupted and the reaction mixture left overnight at room temperature. Then, 2 ml of methanol was added to destroy any unreacted sodium hydride and the solution then concentrated to half of its volume. Ether was added until precipitation of sodium iodide was no longer observed. The solid was removed by filtration and the solvents (ether and 1,2-dimethoxyethane) removed by fractional distillation through a Vigreux column at 200mm. The residual liquid was then fractionally distilled through a smaller column. The pure product (6.25 g), (48%) boiled at 75°C at 127 mm; η_D^{25} , 1.4213. Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.45; H, 10.40. The precursor, 1,2-epoxy-5-hydroxyhexane was prepared, using Sweet and Brown's procedure (39) for epoxidations,

by treatment of 5-hexene-2-ol with m-chloroperoxybenzoic acid in dry ether. The crude material, 95% pure by gas liquid chromatography, was used directly as described above without further purification. The 5-hexene-2-ol was prepared by reduction with LiAlH_4 in ether (79) of commercially available 5-hexene-2-one. Yield, 80%. B.p., 130°C at 710 mm; n_D^{25} , 1.4283. Lit. b.p., 139°C at 752 mm; n_D^{24} , 1.4286 (100).

2-Methyltetrahydropyran was prepared by reduction at room temperature(76) of the previously prepared 6-methyl-4,5-dihydropyran with hydrogen at 500 p.s.i. over freshly made Raney nickel (78), using methanol as solvent. The reaction mixture was left overnight, and then the Raney nickel removed by filtration and the filtrate fractionally distilled. Yield, 75%. B.p., 98°C at 710 mm; n_D^{25} , 1.4210. Lit. b.p., 101°C at 758 mm; n_D^{25} , 1.4217 (101).

3-Hydroxytetrahydropyran. Dry tetrahydrofuran (500 ml), 16.8 g (0.2 mole) of 4,5-dihydropyran and 7.5 g (0.2 mole) of sodium borohydride were placed in a 1 l, three-neck flask provided with a condenser, stirrer and dropping funnel. The flask and contents were kept at 0°C with an acetone bath containing some dry ice, while a solution of 28.7 g (0.2 mole) of boron trifluoride etherate in 200 ml of tetrahydrofuran was added dropwise to the cold stirred mixture. The reaction mixture was left overnight at room temperature and then 135 ml of 3N aqueous sodium hydroxide and afterwards 50 ml of 30% hydrogen peroxide were added dropwise, so that the temperature of the reaction mixture remained at 5°C . When the addition

was completed, the organic layer was separated and the aqueous solution extracted ten times with 200 ml portions of chloroform. The chloroform solutions were combined and dried (MgSO_4), then freed from solvent to yield 13 g of an oil showing by gas liquid chromatography four peaks of equal intensity. This oil was fractionated by distillation giving 3 g of a substance boiling at 100°C at 12 mm; η_{D}^{25} , 1.4570. Lit. b.p., $92-95^\circ\text{C}$ at 12 mm; η_{D}^{21} , 1.4571 (102). Anal. Calcd. for $\text{C}_5\text{H}_{10}\text{O}_2$: C, 58.80; H, 9.87. Found: C, 59.10; H, 9.73.

3-Methoxytetrahydropyran was made by methylation of the 3-hydroxy-tetrahydropyran as described for the preparation of the 6-methoxymethyl-4,5-dihydropyran. Yield, 85%. B.p., 145°C at 710 mm; η_{D}^{25} , 1.4480. Anal. Calcd. for $\text{C}_6\text{H}_{12}\text{O}_2$: C, 62.04; H, 10.41. Found: C, 61.96; H, 10.03.

2-Methoxymethyltetrahydropyran was prepared by room temperature reduction of a methanol solution of 6-methoxymethyl-4,5-dihydropyran with freshly made Raney nickel (78) at 55 p.s.i.. The reaction mixture was left in the hydrogenator for 3 days under these conditions. The Raney nickel was removed by filtration and the product obtained by fractional distillation of the filtrate. Yield, 50%. B.p., 33°C at 13 mm; η_{D}^{25} , 1.4315. Anal. Calcd. for $\text{C}_7\text{H}_{14}\text{O}_2$: C, 64.58; H, 10.84. Found: C, 64.99; H, 10.95.

VI. Reduction of the Tetrahydropyranyl Ethers With Lithium Aluminum Hydride and Aluminum Chloride.

The reduction procedure used during the course of this work was the same for all of the tetrahydropyranyl ethers. As an example, the reduction of the 2-ethoxytetrahydropyran is given below.

Lithium aluminum hydride (1.47 g, 0.0387 mole) was dissolved over a period of about 15 min in 31 ml of anhydrous ether. To this stirred solution was added 4.81 g (0.037 mole) of 2-ethoxytetrahydropyran. Dry aluminum chloride (5 g, 0.0375 mole) was dissolved in 44 ml of dry ether first cooled to -5°C , and this solution was added to the mixture of lithium aluminum hydride and acetal during a period of about one minute. Then the reaction mixture was stirred for 12h at room temperature. The mixture was cooled to $>0^{\circ}\text{C}$ with an acetone bath containing some dry ice. Water (2 ml) then 2 ml of 15% aqueous sodium hydroxide, and finally 2 ml of water were added dropwise. This addition was done as fast as the reaction permitted (5 minutes). This mode of destroying the hydride complexes produced a granular precipitate of aluminum hydroxide that was readily removed by filtration. When necessary the precipitate of aluminum hydroxide was stirred with chloroform or its suspension in water continuously extracted with ether overnight in a liquid-liquid extractor in order to increase the recovery of organic materials. The ethereal filtrate was dried over anhydrous sodium carbonate. Removal of the solvent was accomplished by careful fractional

distillation to avoid losses of products in the distillate. This was checked by g.l.c. analysis of the distillate. The residual oil was found by gas liquid chromatography to be a mixture of ethanol, tetrahydropyran and 5-ethoxy-1-pentanol, with the latter two in a ratio of 2:3.

VII. Reduction Accomplished by the Species AlClH_2 ; e.g. Reduction of 4-methyl-1,3-dioxolane.

LiAlH_4 (0.214 g; 0.0056 mole) was dissolved over a period of 15 min in 4.0 ml of dry ether. To this solution, dry aluminum chloride (0.665 g, 0.005 mole) dissolved in 5.3 ml of cold (-5°C) of dry ether, was added dropwise over a period of 20 seconds. This mixture was stirred for approximately 10 min and then 0.44 g (0.005 mole) of the 4-methyl-1,3-dioxolane dissolved in 0.5 ml of ether was added. The reduction mixture was stirred for 90 min at room temperature and then the hydride destroyed as explained immediately above for the reduction of the 2-ethoxytetrahydropyran. The granular precipitate of aluminum hydroxide suspended in water was extracted continuously with ether overnight in a liquid-liquid extractor. The ethereal extract was dried over magnesium sulfate and removed by careful fractional distillation. The residual oil was analyzed by gas liquid chromatography with the results as shown in Table I

VIII. Competitive Reductions of Mixtures of Dioxanes and Dioxolanes.

In these cases the same procedure as in (VI) was used, except that in this case an equimolar mixture of the dioxane and dioxolane was used as the substrate to be reduced. The results are shown in Table VIII

IX. Reduction by the Species AlH_3 ; e.g. Reduction of 2-Phenyl-1,3-dioxane.

The following procedure is an example of the reductions with AlH_3 .

Anhydrous aluminum chloride (0.612 g, 0.0046 mole) was dissolved in 10 ml of dry, cooled (-5°C) ether. This was added to a previously prepared solution of lithium aluminum hydride (0.521 g, 0.037 mole) in 8 ml of ether. The mixture, kept in a closed container, was allowed to stand for 5 min. A solution of 3 g (0.0183 mole) of 2-phenyl-1,3-dioxane in 4 ml of dry ether was then added in about 10 seconds and the mixture was stirred by a magnetic stirrer for 15 min. The reaction was then quenched by the addition of 4 ml of a 15% aqueous solution of sodium hydroxide to the reaction mixture kept cool ($\sim 5^\circ\text{C}$) with an acetone bath containing some dry ice. This addition was done as quickly as the reaction permitted (~ 1 min). The granular solid material was separated by filtration and washed several times with ether to remove the product. The ether extracts and filtrate were combined, dried over magnesium sulfate and then freed from solvent by careful fractional distillation. The residual oil, when analyzed by gas liquid chromatography showed reduction had occurred to the extent of 9%.

SUMMARY

- 1) A study of the hydrogenolysis of substituted 2-alkoxy- or 2-aryloxy-tetrahydropyrans by combinations of LiAlH_4 and AlCl_3 was undertaken.
- 2) It was determined that by the rapid addition of AlCl_3 to a mixture of the acetal and LiAlH_4 all in equimolar proportions, the effective reducing species in these reactions is the aluminum chloro dihydride (AlClH_2).
- 3) A comparative study was made of the reducing abilities of the three possible species obtainable from the mixtures of LiAlH_4 and AlCl_3 . These species are AlH_3 , AlClH_2 or AlCl_2H , depending on the ratio of LiAlH_4 to AlCl_3 used. It was found that the order of ability to hydrogenolyze acetals and ketals is $\text{AlCl}_2\text{H} > \text{AlClH}_2 > \text{AlH}_3$.
- 4) A mechanistic interpretation of the reaction of hydrogenolysis is given, according to which the rate determining step is the formation of an intermediate carbonium ion that subsequently undergoes rapid attack by a hydride ion. Evidence does not support a mechanism involving a four-center transition state.
- 5) The effect of different alkoxy and aryloxy groups at C_2 , as well as the effect of substituents at C_3 and C_6 in the tetrahydropyran ring, was determined in relation to the behaviour of these tetrahydropyrans towards the reduction with $\text{LiAlH}_4/\text{AlCl}_3$. The results were rationalized in terms of polar effects. Accordingly, those products arising from the more stable intermediate carbonium ion, will be produced in larger proportion. The importance of the inductive effect of substituents at C_3 was pointed out.

Electron attracting substituents at this carbon decrease considerably, the rate of hydrogenolysis, and this was explained in terms of the destabilization of the positive charge at C_2 when the formation of the intermediate carbonium ion takes place. The fact that the $-OCH_3$ and $-OH$ groups promoted ring cleavage was explained in terms of nucleophilic assistance of these groups to the rupture of the C_2 -ring oxygen bond.

Although polar effects have been considered to be of primary importance concerning the direction of cleavage and the rate of reaction, the importance of the influence of steric effects have also been considered. However, these effects are only secondary and can be detected in circumstances where polar effects cancel out. Anomalies concerning the pathway of the reaction of hydrogenolysis have been also mentioned for which no clear explanation can be offered at this stage.

6) A comparison was made of the rates of hydrogenolysis of substituted 1,3-dioxanes and 1,3-dioxolanes. 1,3-Dioxolane acetals react faster than do the 1,3-dioxane acetals. The results were the opposite when the substances compared were ketals. The explanation was given in terms of two 1,3-carbon, hydrogen diaxial interactions present in the 1,3-dioxane ketals but absent in the 1,3-dioxolane ketals.

7) The similarity between acid-catalyzed hydrolysis of acetals and Lewis acid catalyzed hydrogenolysis of acetals was pointed out.

8) Several attempts were made to hydrogenolyze methyl 2,3,4,6-tetra-O-methyl- α -D-glucopyranoside and 2-deoxy-3,4,6-tri-O-methyl- α -D-gluc-

pyranoside. It was found by gas liquid chromatography that the second pyranoside reacted faster, though the products obtained from the hydrogenolysis of the second glycoside were not identified. According to the gas chromatographic analysis of the products obtained from hydrogenolysis of the first pyranoside, it would seem that the preferred route of cleavage was that of ring opening.

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